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OCCURRENCE OF SYMPTOMS OF SICKLE CELL DISEASE IN THE ABSENCE OF PERSISTENT ANEMIA *

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THE occurrence of bone and joint pain, abdominal pain, jaundice and other symptoms in patients with sicklemia has generally been associated with the presence of persistent anemia. According to general belief, individuals who are found to have the sickle cell trait in the absence of anemia do not subsequently develop manifestations of the disease. On the other hand, persons with sickle cell anemia are not believed to undergo remissions so complete that the blood picture becomes normal.[1]

In 1929 Levy [2] reported three cases of supposed sickle cell disease with periods of symptoms and anemia followed by intervals in which normal or near-normal blood counts were obtained. However, his data are not adequate for satisfactory evaluation. Bauer [3] in 1940 suggested that sickle cell anemia might better be called sickle cell disease, because anemia, though the best known and most frequent sign of the disease, is not necessarily the most important one. He thought that the phenomenon of vascular occlusion with production of symptoms of this disease could occur independently of anemia as a result of the sickling tendency. Bauer and Fisher [4] reported two cases of sickle cell disease in which serious consequences of the sicklemia had occurred in the absence of anemia. One of these cases was later reported in detail by Canby, Carpenter and Ellmore.[5] Abel and Brown [6] reported the occurrence of massive infarction of the kidney in a patient with sickle cell disease with only slight anemia, readily explained by the gross hematuria. Sickling could not be demonstrated in the peripheral blood, but great masses of sickled cells were found obstructing the renal vessels.

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Thompson, Wagner and MacLeod [7] reported a fatal case, with death caused by cerebral thrombosis associated with sicklemia in the absence of anemia.

The purpose of this report is to emphasize the occurrence of sickle cell disease with severe symptoms but without persistent anemia. The cases to be presented demonstrate clearly that patients may have sickle cell disease without anemia or jaundice but at times have severe "crises" during which there may or may not be evidence of a marked increase in blood destruction.

Case Reports

Case 1. A 50 year old colored male steelworker has been seen repeatedly at the Johns Hopkins Hospital over a period of 14 years for recurrent episodes of abdominal pain. One brother died at age 20 of "rheumatism." The patient had "rheumatism" starting at age 12, with intermittent aching in the knees and thighs. In adult life these symptoms have been infrequent and of mild degree. He has been able to perform hard work without fatigue or dyspnea. At about age 26 he had an attack of abdominal cramps, subsiding in several hours, followed by at least two similar attacks within a few years. When he was 31 he developed an acute attack of right lower quadrant pain and was hospitalized for "appendicitis." The pain subsided on treatment with ice bags. Three months later he was again hospitalized for a "ruptured appendix." His appendix was removed at that time. He was then well until age 34, when he suddenly developed severe abdominal pain. He was again subjected to laparotomy, but apparently the cause of his symptoms was not identified.

He was first admitted to the Johns Hopkins Hospital in 1934, at the age of 35, because of severe cramplike periumbilical pain of several hours' duration. The pain extended to the epigastrium and lumbar region, and radiated down both thighs. He was nauseated but did not vomit. He was obviously in great distress. The temperature was 99.4° F. (oral). There was no pallor or jaundice. Physical examination revealed generalized boardlike rigidity of the abdomen, with tenderness both direct and rebound. The white blood count was 13,000 per cu. mm. He was thought to have a perforated peptic ulcer, and therefore was immediately operated upon. The only abnormal finding was a nodular, firm, slightly enlarged spleen, which suggested to the surgeon the possibility of sickle cell disease. Postoperative blood studies gave the following results: hemoglobin 14.0 gm., hematocrit 40.0 per cent, and icterus index 11. Sickling preparations showed complete sickling in 24 hours. The abdominal pain subsided on the third postoperative day, and convalescence was uneventful. (This episode was reported by Campbell [8] in a series of cases of sickle cell disease with abdominal crises.)

During the next 14 years the patient returned to the hospital on five occasions because of the recurrence of abdominal pain. With each episode the symptoms and signs have been essentially the same. The patient is seized with sudden, severe, midabdominal pain, usually radiating to the epigastrium and low back, and sometimes down the thighs. There is associated nausea but no vomiting. Examination reveals low grade fever and sometimes slight jaundice. The abdomen is rigid, with variable tenderness. Morphine is always required for relief of pain, which gradually subsides over a period of several days. The icterus index is elevated (10 to 15) during attacks, but has been found to be normal at other times. The white blood count has been 11,600 to 13,000 during episodes of pain. Sickling preparations during crises show no sickling in 30 minutes, but complete sickling in 24 hours. He has never been observed to be anemic at the onset of an episode of pain, and on one occasion the hematocrit was 51 per cent. However, in April, 1947, when he was seen four

weeks following a crisis, his hematocrit had fallen to 35.5 per cent, with hemoglobin 11.7 gm.

In June, 1948, he returned complaining of generalized aching of the joints, with severe pain in the left shoulder. There was some limitation of motion of the shoulder at that time. The hematocrit was 41 per cent. His symptoms subsequently subsided.

When last seen, in September, 1948, he was asymptomatic and felt perfectly well. He was performing heavy work in a steel mill without fatigue or other symptoms. He was a well built, muscular man who did not display the habitus often seen in patients with sickle cell disease. There was no evidence of ulcerations on the legs. The retinal vessels were not unusually tortuous. The heart was not enlarged, but there was a soft, blowing, apical, systolic murmur. The blood pressure was 145 mm. Hg systolic and 100 mm. diastolic. The spleen and liver were not palpable. The remainder of the physical examination was not remarkable. Complete blood count at that time was: red cell count 5.47 million, hemoglobin 12.0 gm., hematocrit 39 per cent, MCV 71, MCH 22, and MCHC 31. The sedimentation rate was 3.0, icterus index 9.0, and white blood count 4,750, with a normal differential. Chest roentgenogram revealed increased vascular markings, and the heart was at the upper limits of normal in size. There was some coarsening of the trabeculae of the ribs. Roentgenograms of the long bones showed suggestive sclerosis of the heads of the humeri, thought to be compatible with sickle cell disease. An electrocardiogram was interpreted as normal, with a PR interval at the upper limits of normal.

Case 2. A 22 year old white male has been seen on numerous occasions at the Johns Hopkins Hospital since December, 1947. He was born in Greece of apparently pure Greek parentage. A brother died at age seven of "anemia." Members of the mother's family were said to have a blood disease. A maternal uncle was found to have sicklemia but no anemia, and was in good health. Since the age of five the patient has had recurrent episodes of bone and joint pain, which have been increasingly severe in recent years. In 1942 he was admitted to another hospital and the diagnosis of sickle cell disease was established. He was subsequently re-admitted on four occasions with severe pains in the extremities.

He was first seen at the Johns Hopkins Hospital in December, 1947, because of severe pain in the right thigh of three days' duration. Physical examination revealed none of the features of the habitus often associated with sickle cell disease, nor were there evident Negroid characteristics. The sclerae were slightly jaundiced. The heart was normal except for a short, soft, apical, systolic murmur. The tip of the spleen was just palpable. Examination of the right thigh showed no objective evidence of local bone or joint disease, and there was no local tenderness or limitation of motion. Laboratory studies were as follows: red cell count 5.64 million, hemoglobin 11.0 gm., hematocrit 38 per cent, reticulocytes 2.0 per cent, MCV 67, MCH 20, MCHC 29, white blood count 18,000, with 68.5 per cent neutrophils. The sedimentation rate was 4.0 and icterus index 35. The serum bilirubin was 3.0 mg. per cent, with 1.2 mg. per cent direct. Urobilinogen was present in the urine in 1:8 dilution. A fresh sickling preparation revealed 100 per cent sickling in 24 hours. An occasional target cell was seen on the smear. An electrocardiogram was normal, with PR interval of .19 second. Roentgenograms of the chest, skull, pelvis and femurs were normal except for increased density of the iliac crests and of the ossification centers of the femurs. He ran a slight fever throughout the hospital stay. The pain disappeared after three days, and he was discharged asymptomatic on the seventh day after admission.

He has been seen on four subsequent occasions for similar attacks of pain, at times occurring in the thighs, wrists, knees, lumbar spine and sternum. Hospitalization has been necessary during three of these episodes. In no instance have there

been local objective signs of bone or joint disease, although pain has been extremely severe, not relieved by morphine. Leukocytosis at times exceeding 20,000 has accompanied the attacks. The serum bilirubin has been slightly elevated during these crises. At the onset of his attacks the red cell counts have varied from 4.58 million to 5.90, hemoglobin 10.5 gm. to 12.4 gm., and hematocrit from 34.5 to 39 per cent. There has been little or no tendency for the hematocrit to fall during and immediately following a period of crisis. However, when seen in an asymptomatic interval, the hematocrit has been as high as 43 per cent. Repeated roentgenograms of the bones have shown no changes from those recorded above. During one episode of crisis the PR interval of the electrocardiogram has been prolonged to .23 second, an abnormality which had not been present on previous tracings. He was last seen in January, 1949, at which time he was completely asymptomatic. The red cell count was 5.77 million, hemoglobin 12.0 gm., and hematocrit 37.5 per cent. The reticulocytes were 2.7 per cent, icterus index 12, and white blood count 12,150, with normal differential.

Case 3. A 24 year old colored female housewife has been seen repeatedly at the Johns Hopkins Hospital over a period of five years. She was first admitted in October, 1943, for secondary syphilis associated with syphilitic meningitis. The family history was noncontributory, and the past history was negative except for preeclampsia with both previous pregnancies. She was given penicillin therapy with rapid disappearance of her luetic manifestations. Blood studies at that time showed: red cell count 5.05 million, hemoglobin 12.3 gm., hematocrit 39 per cent, MCV 77, MCH 24, MCHC 32, icterus index 7, and white blood count 6,500, with a normal differential. Sickling was noted in the counting chamber and verified by wet preparation. She was considered to have the sickle cell trait.

She was again hospitalized in March, 1944, on the obstetrical service for preeclampsia. Delivery was difficult and associated with severe blood loss, although a viable infant was obtained. Following the delivery the hematocrit was 30, and the anemia was attributed to the excessive blood loss. Sickling was again demonstrated, and a red cell fragility test was normal.

About two weeks after delivery she developed severe left upper quadrant pain, chills and fever, and therefore was readmitted to the hospital. She was obviously critically ill, with high fever, rapid respirations and marked pallor. The heart was enlarged, with a soft, blowing, apical, systolic murmur. The spleen was much enlarged and acutely tender, and the liver was palpable. Blood studies were as follows: reticulocytes 9 per cent, red cell count 1.57 million, hemoglobin 3.8 gm., hematocrit 12 per cent, platelets 288,000, white cell count 59,200, and nucleated red cells 25,400. The differential count revealed myeloblasts 1 per cent, undifferentiated myelocytes 4 per cent, differentiated myelocytes 3.5 per cent, juvenile neutrophils 9.5 per cent, segmented neutrophils 67 per cent, lymphocytes 13 per cent and monocytes 2.0 per cent. The serum bilirubin was 1.6 mg. per cent, with 0.7 mg. per cent direct. The icterus index was 12. A diagnosis of sickle cell crisis with splenic infarction was made. She was given transfusions and oxygen inhalations, and was digitalized. The hemoglobin rose slowly over the next two weeks. The reticulocytes reached a peak of 30.4 per cent on the second hospital day and dropped to 1.0 per cent in two weeks. The white cell count gradually returned to normal, and the nucleated red cells disappeared from the peripheral blood. Scleral jaundice was first noted on the third hospital day, and gradually cleared. Patient was afebrile after the third day, and the left upper quadrant pain disappeared after one week. She was discharged two weeks after admission. Blood studies on the day of discharge showed: red cell count 4.13 million, hemoglobin 10.3 gm., hematocrit 28.2 per cent, and white cell count 6,300, with a normal differential. An electrocardiogram was essentially normal, but a teleroentgenogram of the heart revealed enlargement in both directions.

She was again seen in July, 1944, complaining of pain in the left upper quadrant

of 12 hours' duration. The sclerae were jaundiced. The liver and spleen were palpable, and the spleen was tender. The hemoglobin was 10.0 gm. The pain subsided after one week, and the jaundice gradually cleared over the next month.

She was re-admitted to the obstetrical service in May, 1945, and at that time was seven months pregnant. She was moderately anemic but had no joint or abdominal pains. The hemoglobin was 7.0 gm. She was given three transfusions and discharged. She returned to the obstetrical service in June, 1945, because of preeclampsia. The hematocrit at that time was 21 per cent. She was given two transfusions, and suffered a reaction with hemoglobinuria after the second transfusion. She subsequently gave birth to a living child.

On a routine examination in September, 1945, a blood count revealed: red cell count 5.66 million, hemoglobin 11.5 gm., and hematocrit 35.4 per cent. A wet preparation revealed complete sickling in 24 hours. A few days later she returned complaining of aching pain in both knees for one day. There was tenderness deep in both popliteal fossae, but no objective change. The hemoglobin was 10.0 gm. Four days later the pain had almost subsided, and the hemoglobin was 9.5 gm. Thereafter she apparently remained in very good health until March, 1948, when she again returned because of pregnancy. The hemoglobin at that time was 12.0 gm.

In August, 1948, when about eight months pregnant, she was re-admitted with preëclampsia and anemia, with hemoglobin of 6.4 gm. A few days after admission she suddenly experienced severe cramplike pain in the thighs, followed by similar pains in both shoulders and in the right anterior chest. She was found crying and writhing in pain. There were no local physical findings of note, but her temperature rose to 100.4° F. several hours later. The symptoms largely subsided in 24 hours. Four days after the onset of these symptoms the red cell count was 2.54 million, hemoglobin 5.9 gm., hematocrit 20.0 per cent, and reticulocytes 8.0 per cent. There was 100 per cent sickling in 13 hours in wet preparations. The serum bilirubin was 1.5 mg. per cent, with direct less than 0.8 mg. per cent. The white cell count was 19,050 with a shift to the left, and the nucleated red cells were 23,200 per cu. mm. Fourteen days after the onset of this crisis she spontaneously delivered a stillborn fetus. The hemoglobin was 6.9 gm. immediately postpartum. She gradually recovered from the crisis and delivery, and was discharged.

On a routine return visit one month later the red cell count was 4.75 million, hemoglobin 10.2 gm., and hematocrit 35.8 per cent, and she was asymptomatic. She was last seen in January, 1949, and stated that she had been quite well. The red cell count was 5.08 million, hemoglobin 10.7 gm., and hematocrit 34.7 per cent. The MCV was 69, MCH 21, and MCHC 31. The white cell count was 4,100, and the differential was normal.

Discussion

Serious manifestations of sickle cell disease may occur in individuals who do not show persistent anemia. Persons who appear to have the sickle cell trait, in the absence of anemia or jaundice, may suddenly develop severe "crises." During such crises there are usually leukocytosis and jaundice, but evidence of greatly increased blood destruction may or may not be remarkable. Anemia, at times absent at the onset of the crisis, may develop during the course of the episode. Upon subsidence of the crisis the blood count sometimes returns to normal or near-normal levels, and jaundice may be absent. There is no parallelism between the severity of the symptoms and the rate of blood destruction. It is apparent that the symptoms are not produced by the hemolytic process per se, and it seems likely, as Bauer [3]

suggests, that anemia is simply one manifestation of the sicklemia rather than the major cause of the symptoms. Possibly the crises of sickle cell disease result from the obstruction of small blood vessels by masses of sickled erythrocytes, an explanation now accepted by numerous authors.

Some patients apparently go through childhood without symptoms or anemia, and have their first crisis in adult life. Repeated and severe crises may then occur without the development of persistent anemia and jaundice.

It is of interest that each of our patients constantly showed microcytosis. In the case of the white patient of Mediterranean ancestry, there is the possibility of the co-existence of the "Cooley's trait." Silvestroni and Bianco[9] have called attention to the occurrence of constitutional microcytosis in Italian patients with sickle cells and severe anemia. However, in our Negro patients, it seems unlikely that the microcytosis could be explained on that basis.

Delineation between "sickle cell trait" and "sickle cell anemia" is not always possible. Furthermore, the finding of the sickle cell trait cannot be dismissed as of no clinical significance. When symptoms occur in patients with sicklemia, a relationship between the sickling phenomenon and the symptoms cannot be disregarded merely because of the absence of anemia.

Even in the presence of anemia the diagnosis of sickle cell crisis is often difficult. When there is little or no anemia the diagnostic hazards are greatly increased. If such a situation occurs in a white individual, such as the patient reported here, the possibility of inaccurate diagnosis is very great. The diagnostic difficulty is increased by the failure of sickling to occur at times on routine sickling preparations. The use of special technics to enhance sickling should be of assistance in overcoming this problem.[10, 11]

Summary

Three cases are reported in which important manifestations of sickle cell disease occurred in the absence of persistent anemia or jaundice. There was no correlation between the severity of these manifestations and the rate of blood destruction. The "sickle cell trait" cannot always be distinguished from sickle cell disease and cannot therefore be dismissed as of no clinical significance.

Addendum

Since this report was submitted additional studies have been made. The electrophoretic pattern of the hemoglobin of case 1 has been found to be abnormal, but the pattern is not identical with that usually seen in sickle cell anemia or sickle cell trait. These observations will be reported separately. Another patient was observed to develop fatal manifestations of sicklemia in the absence of anemia. This patient, a 54 year old Negro, displayed evidence of diffuse disease of the brain. At autopsy, there were multiple small areas of infarction, with myriads of sickle cells in the blood vessels. A complete blood count prior to death was normal.

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THE CIRCULATION TIME (ARM TO TONGUE TIME) IN LARGE PERICARDIAL EFFUSIONS: AN AID IN THE DIFFERENTIAL DIAGNOSIS BETWEEN LARGE PERICARDIAL EFFUSION AND CARDIAC DILATATION *

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THE diagnosis of pericardial effusion is frequently difficult to establish by clinical methods. Even when roentgen study is included, the diagnosis may not be simple. In small effusions of no more than 300 c.c., the roentgenologic appearance is not sufficiently characteristic to permit its recognition. In moderate sized and large effusions the cardiac shadow may present the pear shape frequently referred to as characteristic. Nevertheless, large effusions may be confused with, and therefore must be differentiated from, an enlargement of the heart. This differentiation presents many practical difficulties. The purpose of this report is to show that the circulation time (arm to tongue) may be of help in this differential diagnosis, particularly if the pericardial effusion is large and caused by an etiologic agent in which the heart is not enlarged (e.g., tuberculosis, stab wounds of the heart and nonspecific pericarditis).

It has been shown by many observers [1, 2, 3, 4, 5, 6] and is common clinical experience that a relationship exists between the degree of cardiac enlargement and the circulation time. In the presence of cardiac dilatation, the circulation time is increased much above the normal; the more marked the dilatation, the greater is the increase in circulation time. Nylin and Malmstrom [6] observed a decided relation between the circulation time and the size of the heart in patients with compensated cardiovascular disease. In 1943 Nylin [3] stated that there appears to be a definite correlation between the circulation time and the size of the heart in compensated cases of cardiovascular disease. More recently he has further explored this relationship [7] and has concluded that the prolongation of the circulation time is not only an expression of the degree of stasis but also of dilatation of the heart and thus of the residual blood of the heart. In 1946 Gernandt and Nylin [1] concluded that in both compensated and decompensated heart disease there is a statistically verified correlation between the heart volume and the amount of residual blood and the circulation time as determined by the first taste sensation. In 1947 Meneely and Chestnut [5] observed a highly significant cor-

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relation between the heart size and the circulation time in 41 patients with heart disease. They concluded that the circulation time is proportional to relative heart volume in patients with heart disease, and thus confirmed the earlier formulation of Nylin. Nathanson and Elek [2] (1947) studied 70 compensated cardiacs with various types of cardiac pathology. They found that there exists a definite relationship between the degree of cardiac enlargement and the circulation time. They observed a definite prolongation of the circulation time as the size of the heart increased. Our experience is similar to that quoted above, namely, that in the presence of cardiac enlargement accompanied by dilatation there is an increase in the circulation time (arm to tongue), and that this increase is to some degree related to the degree of increase in heart size.

Since in many varieties of pericardial effusion the heart itself is not enlarged, it seemed desirable to determine the circulation time in a group of these patients with large effusions; in view of the established relationship between heart size and circulation time, it seemed quite possible that the circulation time might be normal in the presence of large effusions with small hearts.

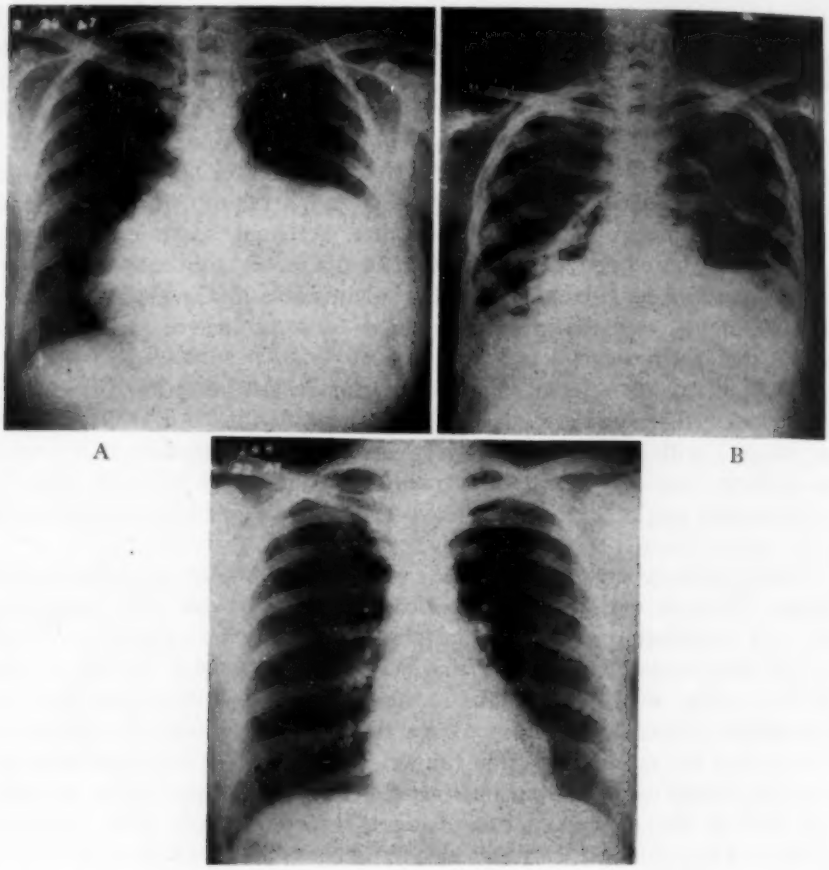
This report is based upon the study of 16 patients with large pericardial effusions and one with adherent pericardium * in whom the circulation time † was recorded. The cardiothoracic ratio ranged from 60 to 90 per cent. In 11 of these patients the circulation time was 16.0 seconds or less at the time of the initial examination; these patients included those with effusions due to tuberculosis, following a stab wound, or nonspecific infections. In three cases the circulation time ranged from 18.0 to 22.0 seconds at the time of the initial examination, but returned to normal after slight decrease in the size of the effusion; these patients included those with effusions secondary to hypertensive cardiovascular disease with effusions of unknown etiology, metastatic neoplasm and adhesive pericarditis. These normal to slightly increased circulation times were obtained in spite of the considerably enlarged cardiac silhouette (figure 1).

The diagnosis of pericardial effusion was confirmed by pericardial tap in 11 patients and by necropsy in three patients; necropsy in one patient revealed a moderately thickened adherent pericardium. In two patients, clinical, roentgen and electrocardiographic studies were characteristic of pericardial effusion. Subsequent clinical improvement with decrease in size of the cardiac silhouette was observed in both of these cases. The actual size of the heart was established by removal of fluid and injection of air, by serial roentgen-ray films as the patient improved, or by necropsy.

The etiology of the pericardial effusion in these patients was as follows:

* Not infrequently the configuration of the cardiac silhouette in adherent pericardium is similar to that of a pericardial effusion. This is particularly apt to occur if the pericardium is thickened.

† The following substances were used in the measurement of the circulation time: Decholin, 10 per cent calcium gluconate, and a 10 per cent solution of strontium bromide. The circulation time with the use of these three substances is approximately the same.



A B C

FIG. 1. Case 9, white, female, aged 42, was admitted to the hospital with a pericardial effusion which was diagnosed as being of the nonspecific type. A. Note large size cardiac silhouette due to pericardial effusion. The transverse diameter of the heart was 21.5 cm., of the chest 27.6 cm. The cardiothoracic ratio was 79 per cent. The circulation time was 15 seconds. B. March 29, 1947, after removal of 1,800 c.c. of serosanguineous fluid, note normal size of the heart. C. April 22, 1947, after absorption of pericardial effusion, note normal size of cardiac silhouette. Circulation time was 13 seconds.

tuberculous pericarditis, proved at necropsy, three cases; tuberculous pericarditis confirmed by the clinical findings (tuberculosis of lungs, sputum examination, or recovery of organism in pericardial fluid), four cases; probable tuberculous pericarditis, four cases; nonspecific, three cases; adhesive pericarditis following pneumonia, one case; hemorrhagic pericardial effusion following a stab wound, one case; neoplastic, one case.

DISCUSSION

Large pericardial effusions are encountered particularly in tuberculous pericarditis and occasionally in the nonspecific and septic types. In these

TABLE 1

Case No.	Age, Sex, Color	Symptoms	Clinical Diagnosis	Trans. Diam. of Heart (cm.)	Trans. Diam. of Chest (cm.)	Cardio-thoracic Ratio	Circulation Time Arm to Tongue	Necropsy	Remarks
1	E. S. 29 FB	Fever, weight loss, cough, dyspnea, and weakness	TB pericarditis and miliary TB	15.5	25.5	61%	17 sec. 15 sec.	Miliary TB, TB pericarditis, pericardium thickened	Heart normal in size
2	C. D. 24 FB	Dyspnea, weight loss, fever	TB pericarditis with effusion. Clinical and EKG	18.5	22.5	82%	15 sec.	None	Died
3	E. C. 21 FB	Shortness of breath, fever, swelling of legs	TB pericarditis(?). Pericardium tapped, 77 c.c. fluid (air injected), small heart	20.5	24.5	83%	13 sec. 13 sec.	None	Discharged against advice
4	L. E. 28 FB	Shortness of breath, swelling of legs	Adhesive pericarditis secondary to pneumonia	22.0	29.0	76%	19 sec. 22 sec.	None	Operation (Brauer). Biopsy of pericardium was negative for TB
5	E. H. 22 FB	Chest pain, fever, shortness of breath	Pericarditis (TB?) (X-ray, clinical, EKG)	17.5	28.5	61%	10 sec.	None	Discharged against advice
6	E. M. 38 FW	Shortness of breath, precordial pain	Pericarditis (TB?). Tapping, x-ray, EKG	20.0	25.5	73%	16 sec.	None	Improved
7	E. T. 41 FB		Pericarditis TB	19.0	26.5	72%	15 sec.	TB pericarditis	Died
8	M. B. 27 FB	Fever and shortness of breath	Pericarditis (TB?) Tapping, x-ray, EKG	19.0	26.5	72%	15 sec.	None	Died
9	M. B. 42 FW	Fever, precordial pain, shortness of breath	Pericarditis, nonspecific. Tapped, injection of air	21.5	27.6	79%	13 sec. 15 sec.	None	Improved

TABLE I—*Continued*

Case No.	Age, Sex, Color	Symptoms	Clinical Diagnosis	Trans. Diam. of Heart (cm.)	Trans. Diam. of Chest (cm.)	Cardio-thoracic Ratio	Circulation Time Arm to Tongue	Necropsy	Remarks
10	G.N. 20 MW	Weakness, chills, fever and weight loss	TB pericarditis by autopsy	15.0 15.7	27.0 27.0	63%	15 sec.	TB pericarditis. Heart small. Plastic pericarditis	Died
11	G. H. 22 FB	Fever, chest pain, shortness of breath	Pericarditis with effusion (TB?)	14.5	24.2	60%	8 sec.	None	Discharged much improved
12	M. L. 16 FB	Fever, cough, shortness of breath, chest pain	TB pericarditis (sputum and biopsy). Tapped, 1,000 c.c. fluid removed, small heart, hydropneumopericardium	18.0	25.0	72%	18 sec.	None	Died
13	D. S. 47 FW	Fever, shortness of breath, precordial pain	Hypertension, pericardial effusion. (TB?)	24.0	26.4	91%	19 sec.	None	Died
14	S. R. 17 MW	Shortness of breath, fever, precordial pain	Hemorrhagic pericardial effusion following stab wound of heart, congestive heart failure	27.0 25.0	31.5 31.5	85% 79%	18 sec. 15 sec.	None	Discharged improved
15	E. B. 42 FB	Fever, precordial pain, shortness of breath	TB pericarditis (clinical)	20.0	25.5	78%	18 sec.	None	Improved
16	S. J. 15 MB	Shortness of breath, fever	Non-specific or TB	19.0 13.0	23.0 23.0	83% 56%	13 sec. 18 sec.	None	Improved
17	S. A. 46 MW	Asthenia, shortness of breath, precordial pain	Metastatic ca. with pericardial effusion	20.0	26.0	77%	18 sec.	Heart weighed 400 grams. 1,000 c.c. sanguineous fluid in pericardium	Died

forms of pericarditis the heart itself is normal or smaller than normal in size. In the septic type the heart is usually normal or only slightly enlarged. In such effusions, the large cardiac silhouette is made up largely of the pericardial fluid, which may attain a volume of 3,000 c.c. All the patients of our series had large effusions and small hearts; in these patients the circulation time was found to be normal or only slightly increased (table 1). Certainly the circulation time would be expected to be markedly prolonged if the size of the large cardiac silhouette was due to dilatation of the heart. On the other hand, in patients with both pericardial effusions and cardiac dilatation, as in acute rheumatic fever, the circulation time would be increased [8] as one would anticipate.

Summary

1. The circulation time (arm to tongue) is reported in 16 cases of massive pericardial effusion and one case of adherent pericardium. In 11 the circulation time was found to be normal, 16.0 seconds or less, and in three others it ranged from 18.0 to 22.0 seconds.

2. The significance of this finding in the differential diagnosis of a large dilated heart and pericardial effusion is discussed.

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CLINICAL STUDY OF VISCERAL LESIONS AND ENDOCRINE DISTURBANCES IN EIGHT CASES OF DIFFUSE SCLERODERMA *

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THE visceral lesions of diffuse scleroderma have been described by Weiss,[1, 2] Lindsay et al.,[3] Talbott et al.,[4] Barber,[5] Stafne et al.,[6] Bevans [7] and Mathisen et al.[8]

The existing ignorance regarding the etiology of diffuse scleroderma, as well as of some of its clinical, histologic, radiologic and laboratory aspects, makes it necessary and of great interest to describe new cases, with the results of investigations focused on the problems just mentioned above.

The aim of this paper is not only to contribute to the solution of these problems, but also to investigate the endocrine status of patients with diffuse scleroderma, particularly concerning the adrenal glands, since the clinical picture of hypoadrenalism has some similarity to scleroderma.

MATERIAL AND METHOD

Eight patients with diffuse scleroderma were studied. Three of the cases very closely resembled acroscleroderma but, despite their slow evolution, the fact that they presented evident visceral lesions and that they ended fatally in five or six years justified their inclusion in the present study.

In two of the patients a complete endocrinologic study was not made, due to their critical condition. With these two exceptions, all were subjected to the following determinations: complete blood count, determination of blood urea, uric acid, creatinine, glucose, cholesterol, calcium, phosphorus, phosphatase, potassium, sodium, chlorides, proteins, carotene and ascorbic acid, Kahn, Wassermann, and Mazzini tests, glucose tolerance and Kepler tests, basal metabolic rate; 17-ketosteroids, follicle stimulating hormone and estrogen excretion in urine. Radiologic studies of the chest, digestive tract and bones and joints were made, electrocardiograms taken and skin biopsies performed. Only in certain cases were the digestive juices and urinary excretion of thiamin investigated. The majority of the cases were hospitalized at the Instituto Nacional de Cardiología or at the Hospital de Enfermedades de la Nutrición so that they could be adequately studied.

RESULTS

Because of the difficulty encountered in presenting the complete picture of each case, the studies are summarized in tables.

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CHART I

Study of the Clinical Picture in Eight Cases with Diffuse Scleroderma

No.	Sex	Age	Illness Duration	Raynaud Manifestations	Digestive Manifestations	Cardiac Manifestations	Pulmonary Manifestations	Joint Manifestations	Calcinosis
1	F	48	5 years	++	+++	+++	+	++	+
2	F	36	6 years	+++	+++	++	+	+	++
3	F	25	7 years	++	+	+	−	+	+
4	F	25	6 years	++	+	+	−	++	+
5	F	39	10 months	+	−	−	−	+	−
6	F	18	2 years	++	++	++	++	++	−
7	M	40	1½ years	+	++	+	+	++	+
8	M	41	1 year	+	+++	+	−	+	−

In seven of the cases there was a diffuse scleroderma involving practically the entire body. Case 5, after 10 months of evolution of the sclerodermatous process, showed lesions confined to the arms.

Chart 1 shows the different clinical symptoms and findings graded as to intensity, with 3 plus being considered the most severe. In seven cases, vascular phenomena of the Raynaud type appeared after or at the same time as the skin lesions, and in one case they antedated the skin lesions. In chart 2 are tabulated the gastrointestinal symptoms and the radiologic findings. Figures 1 to 4 show these alterations. In the majority of the patients, the radiologic study showed a dilatation of the esophagus, the stomach and the small bowel. Radiologically demonstrable lesions of the small bowel have received little or no attention in the literature, but in our cases they were a very striking feature. A decrease of the peristaltic movements was a constant finding. Occasionally cardiac or pyloric stenosis was observed. Due to the nature of the pathologic processes involved in sclerodermatous gastrointestinal lesions, the stenosis was assumed to be organic in origin. The mucosa of the stomach was hypertrophied in the fundus and atrophied at the antrum.

CHART II

Study of the Clinical and Radiological Manifestations of the Digestive Tract Lesions in Eight Cases with Diffuse Scleroderma

	Clinical Manifestations				Radiologic Signs				
					Esophagus		Stomach		Intestines
No.	Dysphagia	Abdominal Pain	Nausea and Vomiting	Intestinal Disturbances	Dilatation	Stenosis	Dilatation	Stenosis	Dilatation
1	++	+++	+++	++	++	+	++	+	+++
2	++	++	+++	++	+	+	++	+	++
3	+	−	+	+	−	−	−	−	−
4	+	−	+	+	+	+	+	−	−
5	−	−	−	−	−	+	−	−	−
6	++	++	+	+	X-rays were not taken				
7	+	++	+	+	++	++	+	+	+
8	++	+++	++	++	X-rays were not taken				

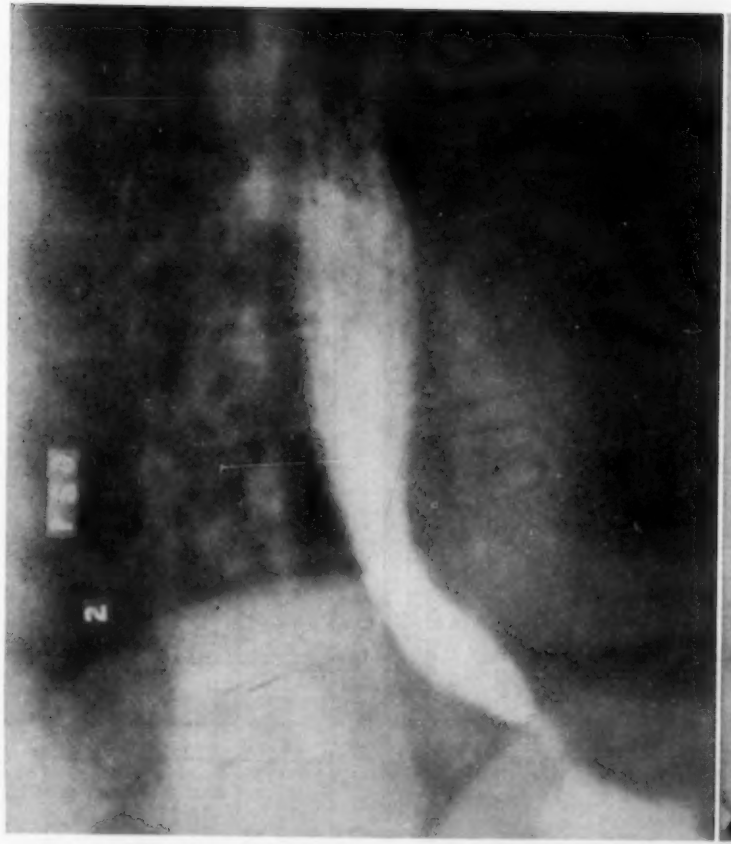

FIG. 1. Dilatation of the esophagus and stenosis of the cardia.

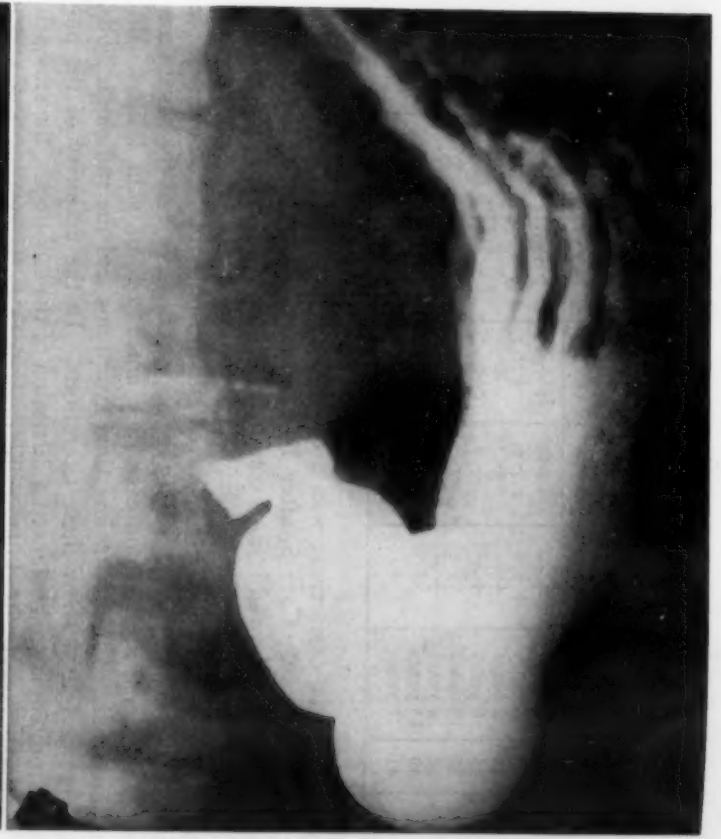

FIG. 2. The stomach is slightly dilated and there is hypertrophy of the gastric mucosal folds.

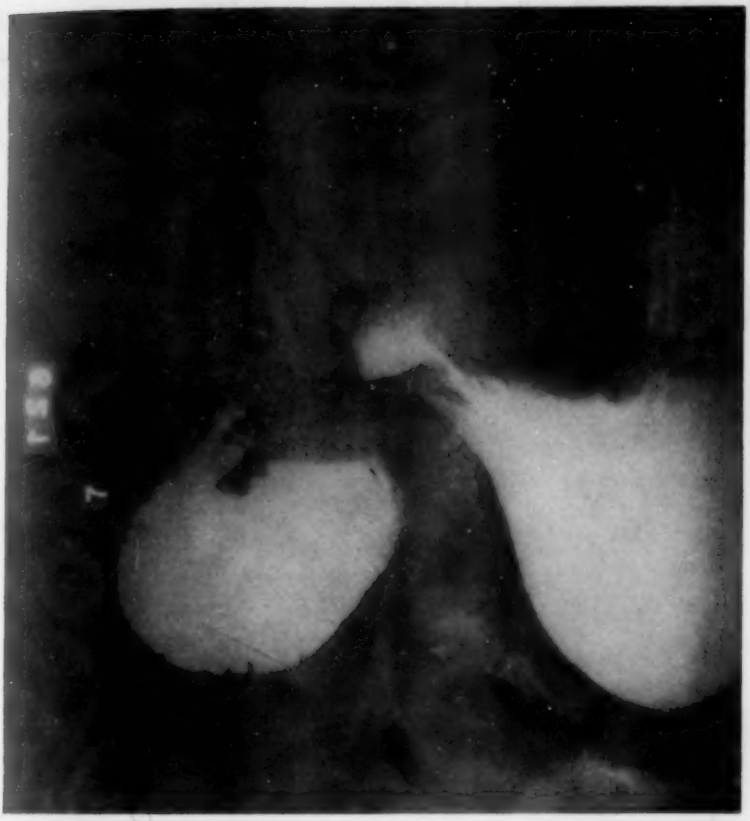

FIG. 3. Enormous dilatation of the third portion of the duodenum.

CHART III

Clinical, Radiologic and Electrocardiographic Study of Cardiovascular Lesions in Eight Patients with Diffuse Scleroderma

No.	Clinical Manifestations						Radiologic Signs	Electrocardiographic Changes	
	Symptoms			Signs					
	Dyspnea	Edema	Liver Enlargement	Palpitations (Lipothymias etc.)	Heart Enlargement	Diminished Heart Sounds	Global Heart Enlargement	Right Bundle Branch Block	Myocardial Changes
1	++	++	+	++	+++	++	+++	+	+
2	++	+	+	+	++	+	++	−	++
3	+	−	−	+	+	+	+	−	−
4	+	−	−	+	−	−	−	+	−
5	−	−	−	−	−	−	−	−	−
6	+	−	−	+	++	++	+	Electrocardiogram was not made	
7	+	−	−	+	+	−	+	+	+
8	+	−	−	+	−	−	−	+	−

Chart 3 shows the clinical cardiac manifestations, as well as the radiologic and electrocardiographic findings. When cardiac enlargement was present it was global, and the radiographic picture was very similar to that of pericardial effusion (figure 5).

FIG. 4. Roentgen-ray of the small bowel shows dilatation of some portions of the jejunum.

The electrocardiographic study of patients with incipient scleroderma showed incomplete right bundle branch block in three cases, and in one advanced case there was right bundle branch block and, in another, extensive auricular and ventricular myocardial lesions.

Curiously, bradycardia was observed in two patients with heart failure.

Radiologic changes in the lungs consisted of slight fibrosis in four cases.

Radiographic study of bones and joints showed marked decalcification of the bony epiphysis in those places where the sclerodermatous process caused the greatest loss of joint mobility, such as in the bones of the fingers (figure 6). However, generalized decalcification was not present, as judged by the study of skulls, alveolar ridge, etc. In fact, in one case, there was a striking increase in the deposition of calcium in the shafts of the metacarpal bones, giving them a marble-like appearance (figure 7).

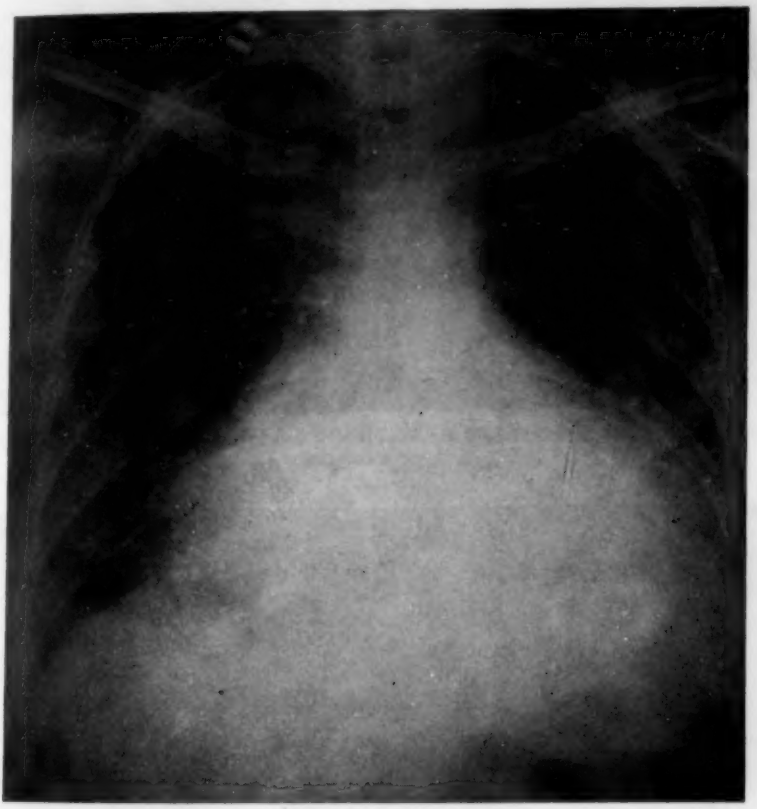

FIG. 5. Global enlargement of the heart.

In spite of the fact that four patients showed clinical manifestations of arthritis, no joint lesions were found in the roentgenographic studies of these patients. In one case there was an increased density of the soft tissues surrounding the joint. Clinically the joint manifestations cleared after weeks or months, leaving no residue.

Chart 4 shows the results of studies of adrenal function in six patients, all of whom showed some evidence of adrenal insufficiency.

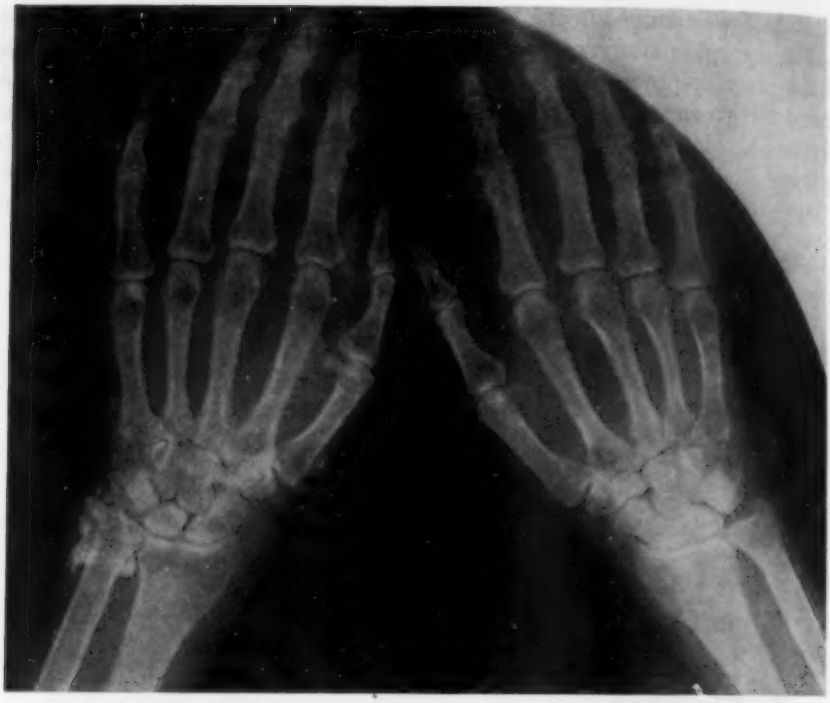

FIG. 6. Slight decalcification of the bones of the hands, no joint changes and soft tissue calcinosis.

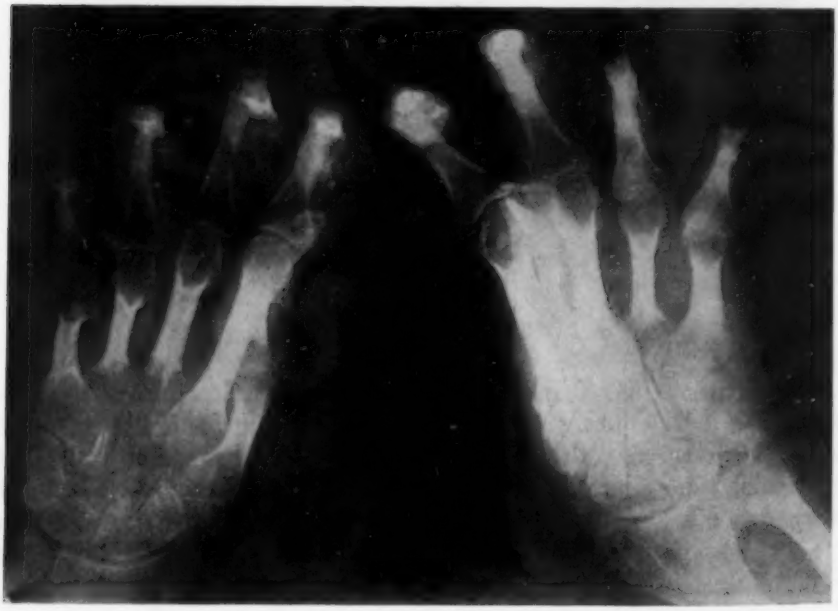

FIG. 7. Decalcification of the carpal and bone epiphysis. Increased density of the diaphysis.

CHART IV

Study of Adrenal Function in Eight Cases with Diffuse Scleroderma

No.	K	Na	Cl	Kepler Test	Glucose	Glucose Tolerance Test	Cholesterol	Proteins		17-Ketosteroids	Lymphocytosis
								"A"	"G"		
1	8.8	140	430	+14	79	Flat	109	3.62	3.56	1.2	24%
2	8.9	99	—	+52	100		87	2.41	3.90	3.4	
3	5.8	152	—	+96	83	Flat	136	3.30	3.23	4.8	39%
4	8.7	140	500	+21	77	Flat	87	4.00	2.18	5.7	40%
5	5.2	150	500	+28	93	Flat	176			2.4	35%
6	Studies were not made in this case										
7	5.00	147	410	+57	83	Flat	175	4.00	3.50	7.4	51%
8	Studies were not made in this case										

Thiamin excretion tests performed in three patients with enormous dilatation of parts of the small intestine were normal. Ascorbic acid and carotene blood levels were performed on all patients, as was urinary excretion of ascorbic acid, and all were normal.

In a few cases a slight decrease in basal metabolic rate or a low calcium blood level was found, but they were not constant even in the same patients. There was no evidence to suggest an alteration in function of the thyroid, parathyroid or gonads.

DISCUSSION

It is unquestionable that scleroderma attacks the entire mesenchymal tissue and may give rise to manifestations in any part of the body.

The clinical picture regarding the digestive tract most commonly found in advanced cases is a progressive dysphagia, with the sensation of a foreign body and a pseudo-obstructive intestinal syndrome, with colicky abdominal pain, abdominal distention, marked diminution of peristalsis, protracted constipation, malaise and restlessness, all of which symptoms subside with bowel evacuation. Occasionally nausea with vomiting of several meals occurs.

We know from the pathologic references and radiologic study of this disease that the above mentioned disorders are due to atrophy of the musculature of the digestive tract, secondary to hypertrophy of connective tissues, with disappearance or decrease of the peristaltic movements, and dilatation of the digestive tract, more specially of loops of intestine. Prostigmine or large doses of vitamin B complex were ineffective in ameliorating the symptoms.

B complex was used in spite of normal levels of vitamin B_1 in the urine of three patients because the nature of the digestive tract lesions observed in these patients was much like that seen in vitamin B deficiency.

Enlargement of the heart is easily explained by the generalized hypertrophy of connective tissue, with myocardial atrophy and subsequent dilatation. Curiously enough, two patients in heart failure exhibited a relative

bradycardia. These two patients also exhibited marked edema, but the portions of the skin affected by scleroderma showed no edema, apparently because of the inelastic character of the sclerodermatous tissues.

Arterial hypotension was also found in most of the patients.

The frequent presence of bundle branch block indicates the extensive myocardial lesions in scleroderma.

The insidious character and the clinical manifestations of heart involvement of irreversible nature are in accord with the assumption that the heart lesions observed in these particular patients were due to scleroderma.

The endocrinologic study of these patients showed the following results:

1. Electrolytic disorders: increase of the serum potassium and positive Kepler test.
2. Decrease in steroid elaboration as judged by the low 17-ketosteroids.
3. Hematologic disorders consisting of lymphocytosis.

All these alterations are common in hypoadrenal activity. The elimination of potassium by desoxycorticosterone is well known, and a positive Kepler test is found in hypoadrenalism.

The diminished steroid elaboration could be due principally to glucocorticoid fraction deficiency. Furthermore, the disturbances of the sugar metabolism, judged by hypoglycemia, flat glucose tolerance curve, etc., may represent a lack of or a diminished production of the S hormone.

Of course, every one of the alterations mentioned indicating adrenal insufficiency may be explained by other means.

In the medical literature there are several reports of cases with diffuse scleroderma where the authors point out the possibility of endocrine disturbances of the thyroid, parathyroid glands, etc. In the eight cases studied in this paper, there were no clinical symptoms or laboratory data to suspect endocrine dysfunction other than hypoadrenalism.

It is of interest that in three cases a hyaluronidase skin test was performed and a large spreading of the enzyme found.[8] This could be due to a diminished adrenal hormone elaboration.

Another point of interest is the therapeutic trial that three of the eight patients were subjected to. Three hundred thousand units of irradiated ergosterol were given daily by mouth to each patient, plus 500,000 units intramuscularly twice a week.

While no modification of the general condition or of the visceral lesions was observed (two of the patients died), the scleroderma of the skin was much improved, not only subjectively but also objectively and by histopathologic studies. Biopsies of the skin were done before and after treatment. The changes observed were softening of the skin, better joint movements and, from the histopathologic point of view, a decrease of the connective tissue proliferation.

It would be very useful to undertake new studies concerning this subject in similar patients with scleroderma in its initial phase.

Summary and Conclusions

Eight cases with diffuse scleroderma were studied from the clinical and laboratory point of view in order to clarify certain clinical manifestations of the visceral lesions and endocrine disturbances caused by this disease.

Among the characteristic clinical changes noted were:

1. Involvement of the digestive tract with mucosal atrophy, absence of peristaltic movements and dilatation of the esophagus, stomach and small bowel, with a fairly characteristic small bowel syndrome.
2. Involvement of the cardiovascular system, with global enlargement of the heart due to connective tissue lesions and subsequent dilatation.
3. Electrocardiographic changes showing incomplete or complete right bundle branch block, or extensive auricular and ventricular myocardial lesions.
4. Heart failure with atypical manifestations, such as bradycardia and absence of edema in the sclerodermatous skin.
5. Joint manifestations without characteristic radiographic changes, and no evidence of chronic joint changes.
6. Bone decalcification of the parts in which mobility of the joints is diminished.
7. Hypoadrenalism, as judged by increased blood potassium, positive Kepler test, low 17-ketosteroids, lymphocytosis, and disturbance of the protein, cholesterol and carbohydrate metabolism.

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CONGESTIVE HEART FAILURE AND HYPONATREMIA: UNTOWARD EFFECTS OF MERCURIAL DIURESIS *

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Recent literature concerning the treatment of congestive heart failure has emphasized dietary salt restriction and the frequent use of mercurial diuretics.[1, 2] In fact, the statement has been made that in severe heart failure mercurial diuretics may be of more importance than digitalis.[3] That these measures hasten the removal of edema fluid and are essential for the proper management of many patients with chronic heart failure has been incontrovertibly demonstrated. Patients with anasarca who are treated according to the regimen advocated by Gold and his associates [1] not uncommonly lose 20 to 25 pounds of weight during the first week of therapy. An integral part of their treatment program is the administration of a mercurial diuretic daily until all visible and occult edema has disappeared, as evidenced by attainment of the "dry weight." The dangers of this type of therapy become more real as the use of mercurial diuretics in this manner in combination with low salt diets becomes widespread. One of the complications incident to the rapid diuresis is a profound change in the electrolyte balance, which may result in distressing symptoms and sometimes even death.[4] It is the purpose of this paper to reëmphasize this complication. The following is an illustrative case.

Case Report

A 58 year old merchant was admitted to the Barnes Hospital in the evening of August 1, 1948, complaining of shortness of breath on exertion. Fourteen years previously he had been told that he had hypertension; however, he had felt well until two years previous to entry when, following an upper respiratory infection, he began to have frequent episodes of coughing and wheezing. Dyspnea on exertion developed and gradually increased. Three weeks before entry he had developed orthopnea and swelling of his legs. For a month he had been taking digitalis and had limited his intake of sodium chloride.

Physical examination at the time of entry revealed a slightly obese, plethoric, orthopneic, cyanotic, acutely ill man. His blood pressure was 140 mm. Hg systolic and 70 mm. diastolic; pulse 100, and respiratory rate 36. The cervical veins were markedly distended. Moderate increase in the anteroposterior diameter of the chest was noted. The diaphragm was low and its excursions were limited. Breath

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sounds were diminished throughout both lung fields. Moist and musical râles were heard over almost all parts of the lungs. The heart was enlarged to the anterior axillary line. The rhythm was regular. A grade 2, blowing systolic murmur was heard at the apex. The pulmonic second sound was accentuated. The abdomen was tense and protuberant. There was moderate shifting dullness in the flanks. Liver dullness extended three fingerbreadths below the right costal margin, but the liver edge could not be felt. A 4 plus pitting edema extended from the thighs downward; a 2 plus pitting edema was present over the sacrum and a 1 plus edema over the lower abdomen.

At the time of entry, the red blood cell count was 5,490,000 per cu. mm. The hemoglobin concentration was 16.1 gm. per cent. The white blood cell and differential counts were normal. The urine contained 1 plus albumin, four to eight white cells per high power field, many hyaline and granular casts, and occasional red blood cells. The blood Kahn test was negative. The venous pressure was 300 mm. of saline, and the circulation time from arm to tongue using decholin was 30 seconds. An electrocardiogram revealed low T waves in Leads I and II and right axis deviation.

The patient was placed on strict bed rest and a bland diet containing 1 gm. of sodium chloride per day. No salt substitute was prescribed. He was given 2 gm. of chloral hydrate soon after admission. During the next few hours his dyspnea in-

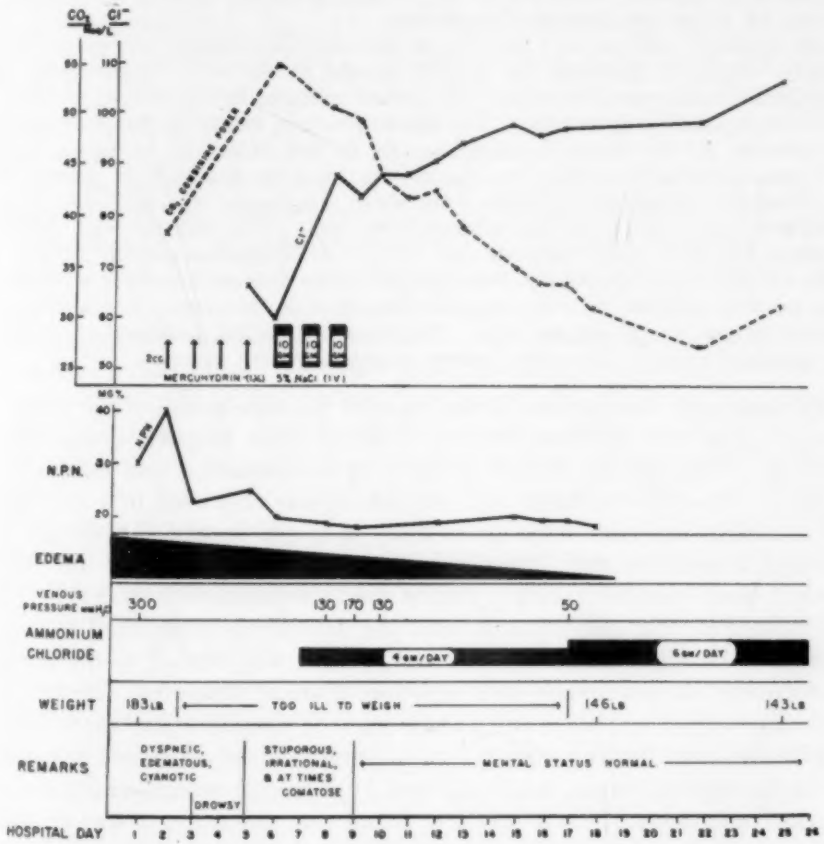

FIG. 1. Symptomatic and electrolytic changes encountered in case 1.

creased, and at 1 a.m., morphine, .01 gm., and atropine, .0004 gm., were given subcutaneously. Thereafter the patient slept soundly until 7 a.m., but his dyspnea and cyanosis remained severe. At 10 a.m., when he was placed in an oxygen tent, he appeared drowsy and lethargic. The blood non-protein-nitrogen at this time was 30 mg. per cent. At 8:30 p.m., 2 c.c. of meralluride sodium solution (Mercuhydrin) were given intramuscularly. The patient slept soundly that night, but at 5 a.m. the nurse noted that his color was poor and that she could not rouse him. When he was seen shortly afterwards by the house officer he was comatose. A left facial weakness was present and all extremities were flaccid. At this time the plasma carbon dioxide capacity (reported later) was 38.1 mEq. per liter, and the blood non-protein-nitrogen was 38 mg. per cent. Lanatoside C, in the dose of 0.4 mg., and 2 c.c. of Mercuhydrin, were given intravenously. Following this the patient regained consciousness, but his sensorium remained clouded. At 4 p.m. a second dose of 0.4 mg. of Lanatoside C was given intravenously. By 7:30 p.m. he had again become irrational and unresponsive and continued so during the next day. On August 5, the fifth hospital day, 2 c.c. of Mercuhydrin were given intravenously, and Lanatoside C therapy was continued. On August 6 the plasma chloride concentration was found to be 67 mEq. per liter and the blood non-protein-nitrogen, 24 mg. per cent. On the following day these values were 64 and 20, respectively. At that time the plasma carbon dioxide capacity was found to be 50 mEq. per liter. During the preceding five days his edema had diminished moderately.

On August 7, 200 c.c. of 5 per cent sodium chloride solution were given intravenously. Figure 1 illustrates the striking changes in electrolyte balance following the sodium chloride administration. The patient tolerated this procedure very well, and it was repeated later that day. The venous pressure, measured frequently during each infusion, did not change significantly. By the end of the day his mental status had improved markedly, and he was able to take small amounts of fluid and medication by mouth. Ammonium chloride, 4 gm. daily, was begun. On August 8, 10 gm. of sodium chloride as a 5 per cent solution were again given intravenously. Following this infusion the lungs remained free of signs of congestion, and no increase in edema was apparent. On August 9 the plasma carbon dioxide capacity was still 49.9 mEq. per liter, and the chloride concentration, 88 mEq. per liter. The blood non-protein-nitrogen was 19 mg. per cent. Thereafter the patient continued to improve, and, simultaneously his electrolyte pattern returned towards normal.

In summary, this patient at the time of his admission to the hospital presented a picture of severe congestive failure, with dyspnea, cyanosis and anasarca. Therapy was aimed at restoring compensation and establishing diuresis. Towards the latter end, salt intake was restricted to 1 gm. daily and mercurial diuretics were given daily in 2 c.c. dosage. Although the patient's drowsiness and lethargy began several hours before the rapid diuresis, these symptoms were probably due to sedation with chloral hydrate and morphine. As diuresis continued the drowsiness progressed to coma. Because we thought that the coma was in some way related to the cardiac insufficiency, we continued with vigorous diuretic measures. It was not until three days later, when the plasma chloride concentration was found to be 67 mEq. per liter, that the true pathogenesis of the coma was suspected. When the hypochloremia was confirmed by a second determination and an extreme retention of bicarbonate was found concomitantly, it was apparent that therapy would have to be directed not toward maintaining rapid salt

and water excretion but toward replacing salt which had been lost during the preceding diuresis. Since the extracellular fluid was presumed to be hypotonic, 5 per cent sodium chloride solution was administered rather than physiologic saline. It is noteworthy that during infusion of this hypertonic saline there was no constant or significant elevation of venous pressure. Clinical improvement closely paralleled restoration of electrolyte balance.

In this and subsequent cases of congestive heart failure treated with salt restriction and mercurial diuretics, we have found a surprisingly high incidence of extracellular fluid sodium and chloride depletion.

Table 1 summarizes the essential clinical and laboratory data in a group of unselected cases with congestive heart failure who were treated in this manner.* In these patients diuresis was usually accompanied by a fall in plasma sodium and chloride and a rise in bicarbonate, potassium and non-protein-nitrogen. It will be noted in table 1 that in case 3 the combined values for CO_2 capacity and plasma chloride exceed the value for sodium. However, the values cited in each instance are those which deviated farthest from the normal during the period of diuresis. At times the most abnormal values for sodium, chloride and bicarbonate occurred on different days. One of the most consistent changes during diuresis was in the blood non-protein-nitrogen, which rose in 11 of the 12 patients. Cases 2, 5, 7, 8 and 10 received varying amounts of a salt substitute containing lithium, which may have accounted for some of their symptoms.

In these cases we have found it safe and practical to administer 5 per cent sodium chloride solution intravenously. By interposing a three-way stopcock between the venipuncture needle and the infusion tubing, one may determine venous pressure frequently with a manometer attached to the side-arm of the stopcock. The possible danger of increasing the circulating fluid volume too rapidly may thus be circumvented. If the patient is able to swallow sufficient salt and is not vomiting there is no advantage to giving the salt parenterally. The patient's sodium chloride deficit may be estimated if one determines the weight and the plasma sodium concentration. The difference between the patient's plasma sodium concentration and the normal, 142 mEq. per liter, should be multiplied by the approximate volume of the total body water in liters. The result, which represents the total sodium deficit in milliequivalents, may be converted to grams of sodium chloride by multiplying by the milliequivalent weight of sodium chloride, 0.0585 gm. The total body water is about 70 per cent of the body weight in the normal individual.† It is important that sodium chloride be given in divided doses, for in a few of our cases the administration of one-third to one-half the calculated dose has restored plasma sodium and chloride to normal. We have found it practical to administer half the calculated dose the first day, further

* Plasma sodium and potassium determinations were done with the Weichselbaum flame photometer.

† A recent study of body fluid volume using deuterium oxide as an indicator suggested that 53 per cent may be a more accurate figure.[6]

TABLE I

Summary of 12 Cases of Congestive Failure Complicated by Hyponatremia

Patient	Age	Sex	Cardiac Diagnosis	Extent of Edema		Daily NaCl Intake (gm.)	Digitalis	Daily NH_4Cl Intake (gm.)	Mercurial Diuretics (Total dose during week prior to electrolyte imbalance)	Extracellular Electrolytes				Non-Protein-Nitrogen Mg. %			Comment
										Lowest Values After Diuresis MEq/liter		Highest Values After Diuresis MEq/liter					
				Periph.	Pulm.					Na	Cl	K	HCO_3	Before Diuresis	During Diuresis	After Diuresis	
Normal Values										142	103	5	27		15–25		
1. B. K.	58	M	Cor pulmon.	4	3	1	yes	0	8 c.c.	—	64	—	50	30	38	19	See figure 1
2. N M.	59	M	Hypertensive cardiovasc. disease; recent myo. infarct.	0	2	2	yes	0	5 c.c.	130	79	4.7	38.5	29	56	—	Cardiac psychosis during terminal 2 weeks, ?aggravated by electrolyte changes
3. M. B.	77	M	Arteriosel. heart disease	0	4	2	yes	0	6 c.c.	131	100	4.4	33.9	28	33	—	No symptoms
4. E. G.	65	M	Arteriosel. heart disease	4	2	1	yes	0	2 c.c.	132	—	7.5	—	45	72	38	No symptoms
5. A. A.	54	F	Hypertensive cardiovasc. disease	4	3	1	yes	4	4 c.c.	132	84	5.2	36	21	37	23	Periods of confusion questionably correlated with electrolyte imbalance
6. D. S.	58	M	Rheumatic ht. disease; aortic valvulitis	0	2	3	yes	0	5 c.c.	138	97	4.9	36.9	21	33	21	No symptoms
7. F. M.	49	F	Hypertensive cardiovasc. disease	3	2	2	yes	0	3 c.c.	128	83	4.5	—	33	63	45	Irrational, crying, vomiting during period of salt depletion. Cleared with salt therapy
8. J. K.	57	M	Rheumatic ht. disease; aortic and mitral valv.	0	4	2	yes	0	8 c.c.	125	—	6.8	—	17	33	33	Pt. lethargic, confused, at times drowsy; but these symptoms not correlated temporally with electrolyte imbalance
9. G. C.	47	M	Rheumatic ht. disease; aortic and mitral valv.	0	2	2	yes	4	4 c.c.	128	95	5.6	26.7	25	50	20	See figure 2. Pt. developed symptoms in spite of relatively normal plasma chlorides
10. B. H.	42	F	Hypertensive cardiovasc. disease	2	4	2	yes	0	6 c.c.	116	79	5.8	29.5	28	42	64	Pt. had downward, fatal course. During salt depletion edema was greater, pt. was irrational and in shock. Improved with Rx.
11. M. P.	55	M	Rheumatic ht. dis.; mitral valvulitis	0	2	2	yes	4	6 c.c.	132	99	5.2	—	21	24	24	No symptoms. Plasma chlorides probably normal because of NH_4Cl intake
12. E. P.	58	M	Arteriosel. ht.	4	4	3	yes	4	10 c.c.	137	100	4.9	34	19	18	21	No symptoms

doses to be determined by subsequent sodium and chloride plasma levels. It should be emphasized that although sodium is predominantly extracellular, the hypotonicity produced by sodium deficit is of the same magnitude in the intracellular fluid as in the extracellular fluid. For this reason the total sodium deficit should be calculated on the basis of total body water.[5] In edematous states the total body water exceeds 70 per cent of the body weight, in which case the sodium chloride deficit as calculated above may be too low.

In the case cited above, no such approximation of sodium chloride deficit was attempted. Relatively small quantities of sodium chloride were given cautiously, and frequent determinations were made of the venous pressure, plasma chloride and plasma carbon dioxide capacity.

Discussion

That the diuresis produced by mercurials is due to a direct action on the kidney was ingeniously demonstrated by Govaerts in 1928.[7] Any extrarenal effect, if present at all, has been found to be of little magnitude.[8] Studies by Schmitz,[9] Hermann and Decherd,[10] Blumgart,[11] and Melville and Stehle [12] established the fact that the action on the renal tubules inhibits the re-absorption of water and chloride. Keith and Whelan,[13] Hermann and Decherd,[10] Reaser and Burch,[14] Griggs and Varner,[15] and Brown and Bradbury [16] have emphasized the inhibition of sodium re-absorption as well. These investigators commented on the fact that urinary sodium and chloride concentrations during mercurial diuresis were sometimes in excess of the plasma concentrations,[9, 13, 14] indicating a greater impairment of sodium and chloride re-absorption than of water. Despite these observations, changes in the plasma electrolytes found by these investigators following mercurial diuresis were irregular and conflicting. DeGraff and Nadler,[17] Crawford and McIntosh,[18] Blumgart [11] and Melville and Stehle [12] found a decrease in plasma chloride concentration following mercurial diuresis. Schmitz [9] and Keith and Whelan [13] found no change in the plasma chloride concentration. None of these workers found a consistent change in the plasma sodium values. Our findings in the limited number of cases studied are at variance with theirs. Both sodium and chloride plasma concentrations dropped to subnormal values during mercurial diuresis in most of our patients. The hyponatremia and hypochloremia occurred irrespective of the presence of severe renal disease. Similar electrolyte abnormalities were observed by Soloff and Zatuchni [4] in patients undergoing treatment for congestive heart failure, and by Stead et al.[19] in hypertensives who were "desalted" with low sodium diets and mercurial diuretics. In several of our patients, reduction in plasma sodium concentrations was associated with a rise in the potassium concentration. Elevation of plasma potassium concentration, probably as a result of migration of potassium from cells to extracellular fluids, has been observed in other conditions involving excessive loss of sodium and water

from the body.[20] In none of our cases was the potassium concentration high enough to produce clinical or electrocardiographic abnormalities.

In patients with well-established congestive failure with edema the extracellular fluid compartment is expanded. This excess fluid is contained mainly in the interstitial spaces, the amount retained in the vascular compartment being by comparison small. The interstitial fluid is isotonic with the blood plasma, being, for practical purposes, an ultrafiltrate of the latter.[21] The removal of the excess fluid in the extracellular space may be accomplished by a combination of a low salt diet and mercurial diuretics. However, as pointed out above, during the excretion of this fluid sodium and chloride are removed at a relatively faster rate than water; consequently, the sodium and chloride values of the extracellular compartment fall, and the fluid becomes hypotonic. This abnormal situation could be corrected by the intake of moderate to large amounts of salt in the diet. However, if, as is usually the case, the intake is limited to 1 or 2 gm. of sodium chloride daily, no correction of this defect can be expected to occur. Subsequent to the hyponatremia and hypochloremia so induced, the urine output becomes low.[21, 22, 23] If mercurial diuretics are given several times at frequent intervals, this chain of events is repeated again and again. The serum sodium chloride becomes depleted, and oliguria ensues. It has been demonstrated that in the presence of subnormal plasma sodium and chloride concentrations the diuretic response to organic mercurials is inhibited.[19] Evans [24] noted that the depletion of the sodium chloride reserves by a permanent biliary

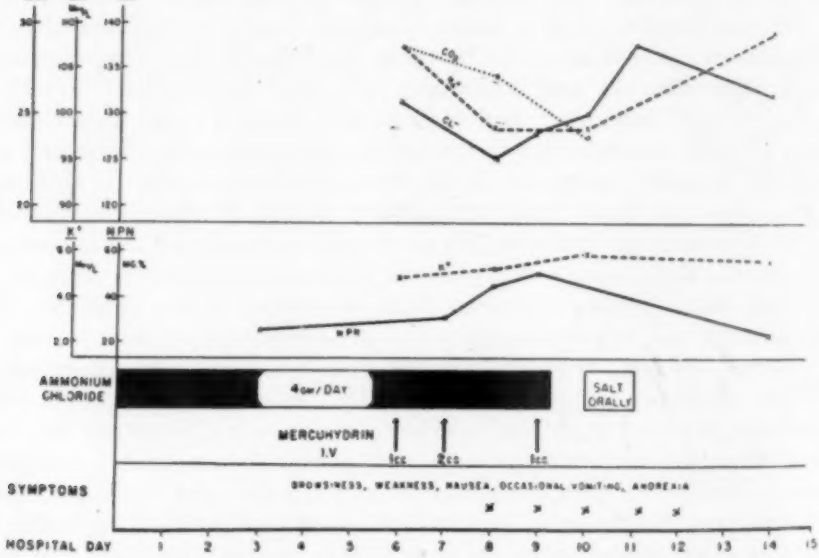

FIG. 2. Symptomatic and electrolytic changes encountered in case 9.

fistula resulted in a diminished diuresis following the injection of salyrgan. Here the diuretic response to mercurials is likewise poor.

Clinically, the situation which at this point presents itself is one of a patient with chronic cardiac failure who, in spite of vigorous treatment, is getting worse rather than better and does not respond to mercurial diuretics. Urinary output is poor, and edema, if present, persists. The symptoms which accompany this state are rather characteristic.[2, 4, 25, 26, 27, 28] During early mercurial diuresis, the patients frequently complain of profound weakness and occasionally of restlessness. These symptoms by themselves are neither alarming nor serious and usually disappear if treatment is not pressed. However, if electrolyte depletion is increased by further diuresis, dizziness, drowsiness, muscular pains and apathy appear. Anorexia may be present and serve to decrease further the sodium intake. Confusion or frank psychosis may appear, to be followed at times by convulsions and coma. If the electrolyte deficit is not corrected, death may result.

These manifestations are strikingly similar to those described for water intoxication.[29] Fundamentally, their pathogenesis is probably the same. Both sodium chloride concentrations in the plasma and interstitial fluid are low. But the predominant rôle of sodium is indicated by the fact that the use of ammonium chloride or calcium chloride as an adjuvant to mercurial diuresis, with consequent maintenance of the plasma chloride concentration at or near normal, does not prevent the development of this syndrome.[25] This fact is well demonstrated in figure 2, which illustrates a case wherein symptoms were prominent while the patient was receiving ammonium chloride.

Summary

1. The administration of mercurial diuretics to patients whose sodium chloride intake is restricted may result in hypotonicity of the body fluids.

2. Usually the electrolyte deficiency does not manifest itself clinically, but occasionally anorexia, apathy, nausea, muscular pains, psychosis and coma are observed.

3. Oliguria and azotemia sometimes occur and may give one the erroneous impression that therapy (i.e., salt restriction and mercurialization) has not been vigorous enough. At such a point more rigid salt restriction and more frequent administration of mercurials are fraught with danger.

4. The symptoms and signs of salt depletion are usually alleviated by the administration of adequate amounts of hypertonic sodium chloride solution.

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LYMPHANGITIC CARCINOMATOSIS OF THE LUNGS: SIX CASE REPORTS AND A REVIEW OF THE LITERATURE *

By THEODORE E. HAUSER, *New York, N. Y.*, and ARTHUR STEER, *San Francisco, California*

ALTHOUGH cancer metastasizes commonly to the lungs, such metastases are usually discrete and not implanted in any definite relationship to blood vessels or lymphatics. In such cases pulmonary symptoms are usually absent or are not a prominent part of the clinical picture. It is relatively uncommon to find diffuse lymphatic permeation of the lungs resulting from a primary carcinoma elsewhere. When this does occur, the pulmonary symptoms usually become the outstanding and frequently the only presenting complaint.

In 1936 Wu [1] reviewed the entire literature on lymphangitic carcinomatosis of the lungs. He stated that this was first described in the European literature by Andral in 1829, and that the paucity of physical signs to account for the distressing symptom of dyspnea was first noted by Troisier in 1874. Up to 1936 at least 70 such cases had been reported, the majority by French and German authors. He was able to analyze 49 published case reports. It was noted that 18 were under the age of 40. Thirty-six of the 49 patients had a primary neoplasm in the stomach. The next most common primary neoplasm was bronchogenic carcinoma, which occurred in five of the cases. Other primary sites which have been mentioned are tongue, pancreas, breast, prostate, uterus, sigmoid colon, liver, gall-bladder and rectum.

The most striking feature in patients with lymphangitic carcinomatosis of the lungs is the symptom-complex of dyspnea, cough, general physical deterioration and cyanosis.[1, 2, 3] The frequency of this clinicopathologic picture has gained recognition in the American literature only within the past 15 to 20 years. In 1936, Jarcho [4] also reviewed the literature and pointed out the occurrence of thrombocytopenic purpura due to bone marrow metastasis. In Schattenberg's [5] case the patient, like many others,[6, 7, 8, 9] had the presenting complaint of shortness of breath and had no complaints referable to the primary neoplasm, which was a scirrhous carcinoma of the stomach. Two case reports of lymphangitic carcinomatosis of the lungs have been published in the New England Journal of Medicine.[6, 8] In one, the patient had an annular carcinoma of the stomach without any gastric symptoms. Lambie and Collier [10] in 1946 reported a patient with broncho-

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genic carcinoma with lymphangitic carcinomatosis of the lungs. In 1947, Sweigert, McLaughlin and Heath [11] reported a carcinoma of the pancreas with pulmonary lymphatic carcinomatosis in a 22 year old white male.

In the past 10 years, there have been six cases of lymphangitic carcinomatosis of the lungs at Fitzsimons General Hospital.

Case Reports

Case 1. A 46 year old white male was treated at Fitzsimons General Hospital for pulmonary tuberculosis from 1918 to 1920. In 1926 he had a two-stage left thoracoplasty. He remained asymptomatic until October, 1937, when he first noted the intermittent presence of blood in his stools. This was accompanied by colicky midabdominal pain and, six months later, was followed by diarrhea which persisted

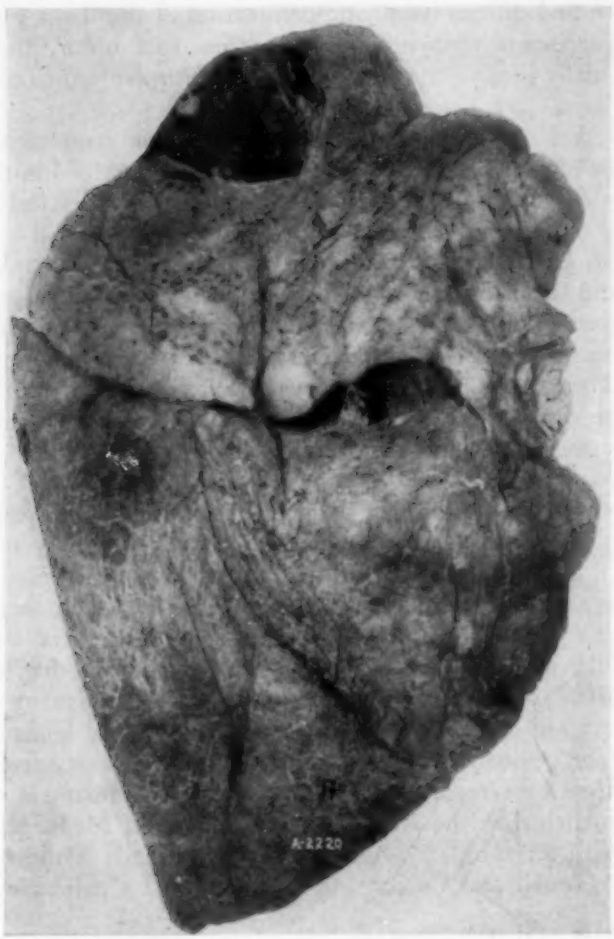

Fig. 1. *Case 1.* External view of right lung. The subpleural lymphatics are prominent and distended with tumor cells (A).

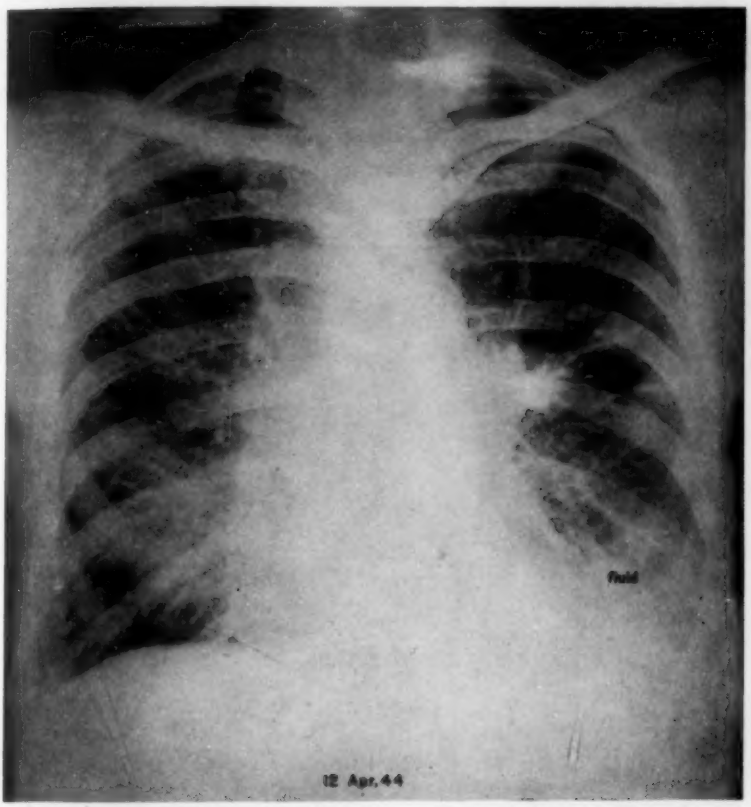

FIG. 2. *Case 2.* X-ray of April 12, 1944, showing diffuse linear infiltration of both lungs with fluid in the left base.

to the time of admission on January 30, 1939. One week before admission he developed severe shortness of breath. Following admission to this hospital, his condition steadily became worse. He became very cyanotic and his hands and feet became edematous. He died on March 5, 1939.

Physical Examination on the Final Admission: His weight was 141 pounds (normal 150). Pulse rate was 120 and blood pressure 140 mm. Hg systolic and 95 mm. diastolic. Rectal examination showed no palpable rectal pathology.

Laboratory Examination: One of four sputum smears for acid-fast bacilli was positive. The red blood cell count was 4,410,000.

A chest roentgenogram revealed left side thoracoplasty. The right lung showed diffuse linear lesions scattered throughout the entire lung field.

Due to a long previous history of pulmonary tuberculosis, the abdominal symptoms of colicky pain, bloody stools and diarrhea, which began in 1937, were attributed to a possible intestinal tuberculosis, although such symptoms are not usual in ulcerative tuberculous ileocolitis.

Significant autopsy findings:

Gross: The right ventricle was hypertrophied and dilated. The patient had a stenosing, infiltrating and ulcerating adenocarcinoma of the proximal portion of the

rectum which had metastasized to the retroperitoneal lymph nodes, peritoneum, liver, left periureteral tissues, producing left hydronephrosis, and to the right lung. The left lung had been compressed by the thoracoplasty for tuberculosis and contained healed tuberculous foci but no tumor. The right lung weighed 1,085 gm., did not collapse even on manipulation, and contained recognizable discrete tumor nodules. The subpleural lymphatics were unusually prominent, and recognizably distended by tumor (figure 1). Cut sections were so peppered with pinpoint tumor foci as to suggest miliary tuberculosis.

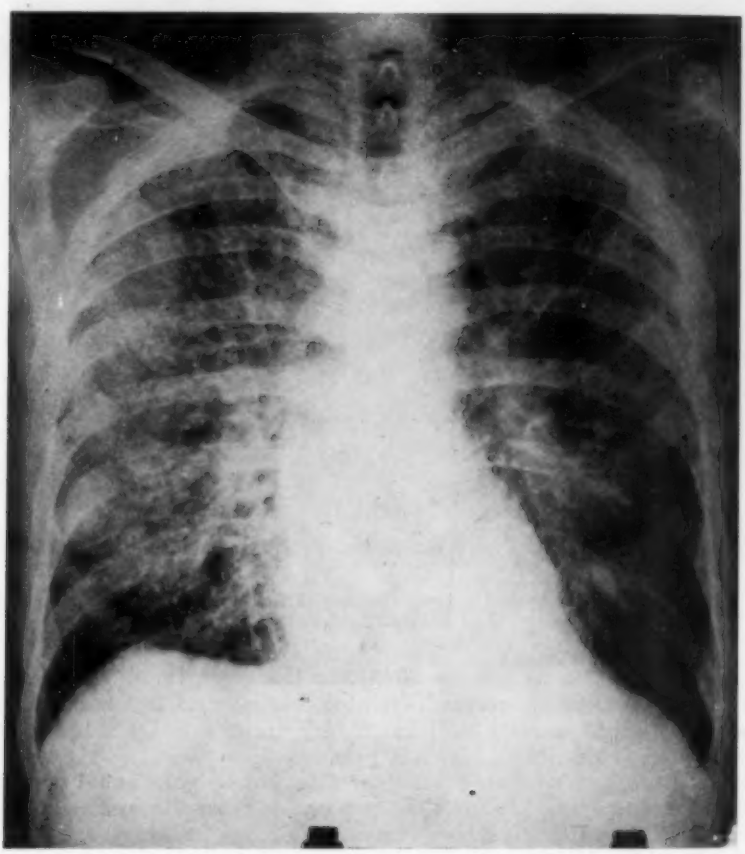

FIG. 3. *Case 3.* Roentgenogram of chest March 4, 1948. In July 1947, a roentgenogram of the chest was negative. The x-ray picture remained unchanged from December 1947 through March 4, 1948.

Microscopic: (Right lung description only.) Lymphatics everywhere contained tumor emboli. Subpleural lymphatics were especially prominent. All were associated with some degree of fibrosis, but this was more prominent where perivascular lymphatics were involved.

Case 2. A 66 year old white male had gastric symptoms for eight months prior to a subtotal gastric resection on November 12, 1943, for carcinoma of the stomach. Following operation he felt well for two months but then noted gastric fullness and mild abdominal pain. About February 1, 1944, he developed an uncontrollable

cough productive of small amounts of white, nonbloody, clear sputum. About April 1, 1944, he developed progressive severe dyspnea. At the time of his admission to Fitzsimons General Hospital on April 9, 1944, he appeared emaciated, was markedly dyspneic, and had a severe persistent cough. Blood pressure was 120 mm. Hg systolic and 84 mm. diastolic, and pulse 92. Breath sounds were generally diminished over the right chest. There was a well-healed right rectus abdominal scar, beneath which was an indefinite adherent mass which did not move on respiration.

A gastrointestinal series showed a well functioning stoma without evidence of local recurrence of the tumor. A chest roentgenogram on April 12, 1944 (figure 2), showed accentuation of the hilus with a fine reticulated stringy pattern throughout both lungs. The costophrenic angles showed blunting, more prominent on the left. Red blood count was 4.8 million, hemoglobin 15 gm., leukocyte count 7,400.

The patient's health deteriorated rapidly and progressively. He coughed incessantly and uncontrollably and he developed anorexia and vomiting. On April 22, 1944, the right jugular vein was thrombosed and six days later the right axillary vein became thrombosed. The patient died on May 8, 1944.

Significant autopsy findings:

Gross: Tumor was still present in what remained of the stomach and had infiltrated the pancreas and peripancreatic tissues by direct extension and had metastasized to the pancreatic, abdominal, aortic and bronchial lymph nodes, to the heart, aorta, left adrenal, spleen and esophagus and diffusely throughout both lungs. The lungs contained prominent fibrous septa and innumerable poorly defined, barely visible nodules.

Microscopic: (Lung description only.) All sections showed diffuse tumor infiltration, predominantly in lymphatic channels but with some tumor cells in blood vessels and alveoli. Subpleural lymphatics were prominent and filled with clumps of tumor cells which appeared to be growing along the lymphatic channels rather than representing tumor emboli. There was a moderate fibrous reaction to the tumor infiltration. In places small and medium sized vessels were surrounded by fibrous bands and had thickened walls.

Case 3. A 48 year old white male was well until November 1, 1947, when he developed a cold, a temperature of 100° F., and right anterior chest pain of a sharp pleuritic type. One week later he developed a nonproductive cough with wheezes in his chest, anorexia and fatigue, and noted a 15 pound weight loss. Because of the progression of these symptoms, he was hospitalized on December 18, 1947, in an overseas hospital. At that time he had a cough productive of 30 c.c. of tenacious, white, nonfoul sputum per day and was markedly dyspneic. A roentgenogram of the chest revealed a diffuse linear, reticular-like pattern throughout all lobes of both lungs (figure 3). He was transferred to Fitzsimons General Hospital with diagnosis of miliary tuberculosis, where he arrived February 7, 1948.

On admission to this hospital he was extremely emaciated and had a rapid, shallow type of respiration. There were medium moist râles heard throughout the chest. There was no cyanosis. Examination of the abdomen was entirely unremarkable. Sputum cultures were negative for acid-fast bacilli. Sputum smears were negative for tumor cells. Cultures for fungi revealed abundant growth of *Candida tropicalis.*

Hospital Course: The patient was placed on streptomycin February 26, 1948, his diagnosis being still uncertain. On February 28, 1948, he had an acute episode of respiratory distress with cyanosis. Physical examination revealed moist bubbling râles throughout both lungs and a blood pressure of 170 mm. Hg systolic and 90 mm. diastolic, with pulse 130 and respirations 40. He responded well to oxygen, aminophylline and digitalis. However, he required oxygen continuously until his death.

At no time did he complain of gastrointestinal symptoms, and although the diagnosis of carcinomatosis was entertained, he was too weak to allow further investigations. He died on March 18, 1948, four months after the onset of his illness.

Significant autopsy findings:

Gross: Patient had an adenocarcinoma at the gastroesophageal junction of the stomach which had metastasized to both adrenals, the pancreas, the pituitary gland, the pleura on the left, the lumbar vertebrae, hilar lymph nodes, and diffusely through-

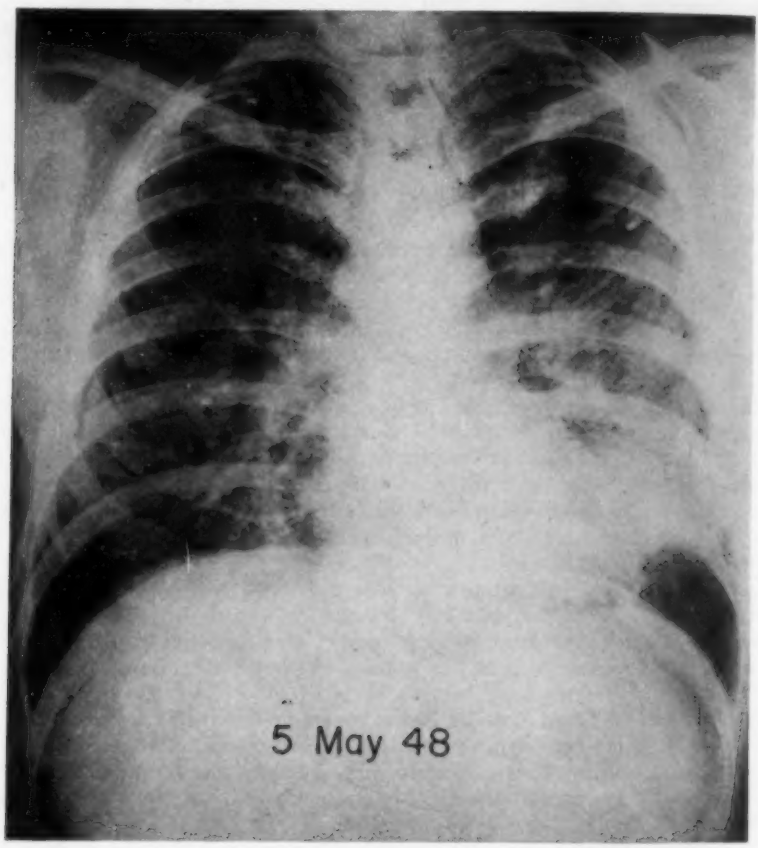

FIG. 4. *Case 4.* Roentgenogram of the chest taken three months after onset of present illness. It reveals confluent infiltration in the left lower lobe with diffuse fine infiltration of the right lung.

out all lobes of both lungs. The right lung weighed 965 gm. and the left 670 gm. Subpleural lymphatics were unusually prominent and contained pinpoint white soft areas along their course. The lungs were firm and noncrepitant, with prominent perivascular fibrosis of small and medium-sized blood vessels. There were no solitary tumor nodules.

Microscopic: (Lung description only.) Sections from all lobes contained small nests of tumor cells, most of which were in lymphatic channels. A few appeared in alveoli. Where perivascular lymphatics were involved there was an associated

fibrosis which decreased the caliber of the lumen of the vessel. Small vessels were especially affected, showing intimal hyperplasia, and some were completely occluded. In some areas alveoli had thickened walls or were completely replaced by the fibrosis associated with the tumor infiltration.

Case 4. A 47 year old white male was well until January 20, 1948, when he developed nausea, diarrhea and abdominal pain, with a temperature of 100° F. which lasted for 36 hours. He was asymptomatic until 10 days later, when he developed a nonproductive cough with right anterior chest pain which was worse on deep breathing and coughing. He also had slight dyspnea on exertion. A roentgenogram taken

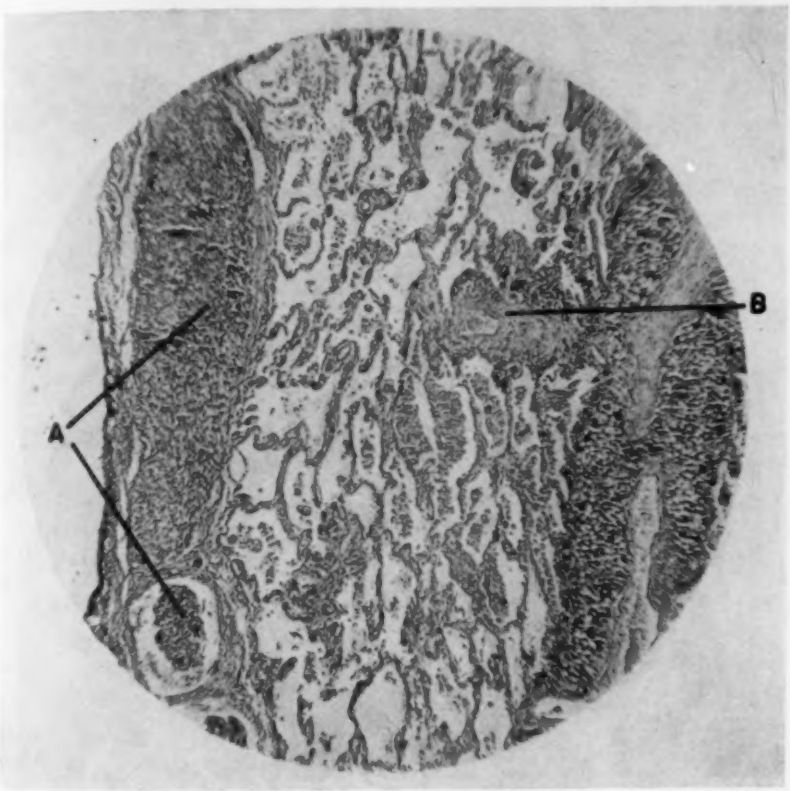

FIG. 5. *Case 4.* A. Tumor distending subpleural lymphatics. B. Perivascular fibrosis of small blood vessel.

the following day showed "atypical pneumonia left base." He continued to work and his symptoms remained unchanged until February 22, 1948, when he had the first episode of blood-streaked sputum; he was hospitalized the following day. At that time he had a slightly productive cough, slight dyspnea, right anterior chest pain and a rapid pulse. He was transferred to Fitzsimons General Hospital on March 26, 1948. Physical examination on admission showed normal weight (170 pounds), pulse rate 100, normal temperature and a blood pressure of 140 mm. Hg systolic and 88 mm. diastolic. The only positive physical findings were many subcrepitant râles over the left lower lung field posteriorly.

Hospital Course: The patient remained afebrile throughout his hospitalization. Roentgenogram (figure 4) revealed diffuse fibrosis throughout both lung fields. There was a moderate amount of soft infiltration in the lower two-thirds of the left lung field. This failed to clear up on penicillin and sulfadiazine. The patient was bronchoscoped on April 30, 1948, and findings were consistent with chronic bronchitis. A biopsy taken from the superior branch of the left lower lobe bronchus showed

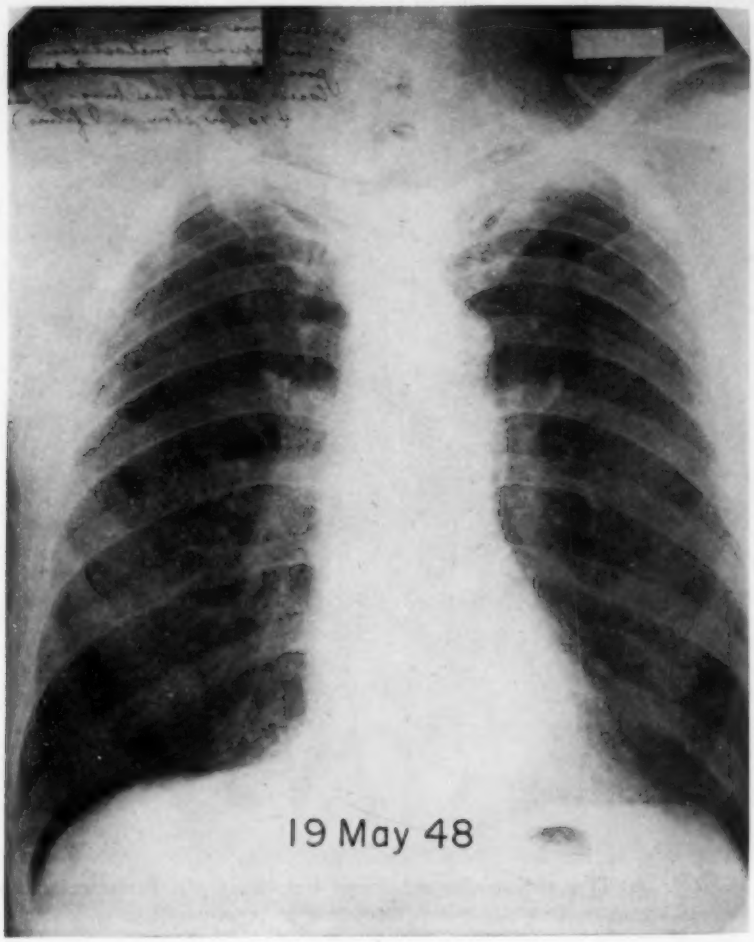

FIG. 6. *Case 5.* Roentgenogram of chest taken May 19, 1948. It reveals evidence of old apical tuberculosis on the right.

chronic bronchitis. By the middle of June the patient had lost 10 pounds. His pulse remained fast, and dyspnea increased. Digitalization was accomplished during June. These symptoms became progressively worse during July, and during the latter part of July sputum examinations revealed cells having the appearance of tumor cells. On July 21, 1948, the patient developed pitting edema of the ankles and feet and dyspnea became worse. An electrocardiogram showed evidence of cor pulmonale.

The patient was started on continuous oxygen which was maintained until his death. By the end of July, he had a weight loss of 30 pounds. He was mentally clear and had no objective neurologic findings. On August 7, 1948, the patient developed pleuritic pain in the left lower chest. A roentgenogram of the chest revealed a spontaneous pneumothorax on the left. On August 29, 1948, the patient had a convulsive seizure of a generalized nature. No paralysis was noted, but there was generalized hyporeflexia. He became gradually weaker and more cyanotic and died September 11, 1948.

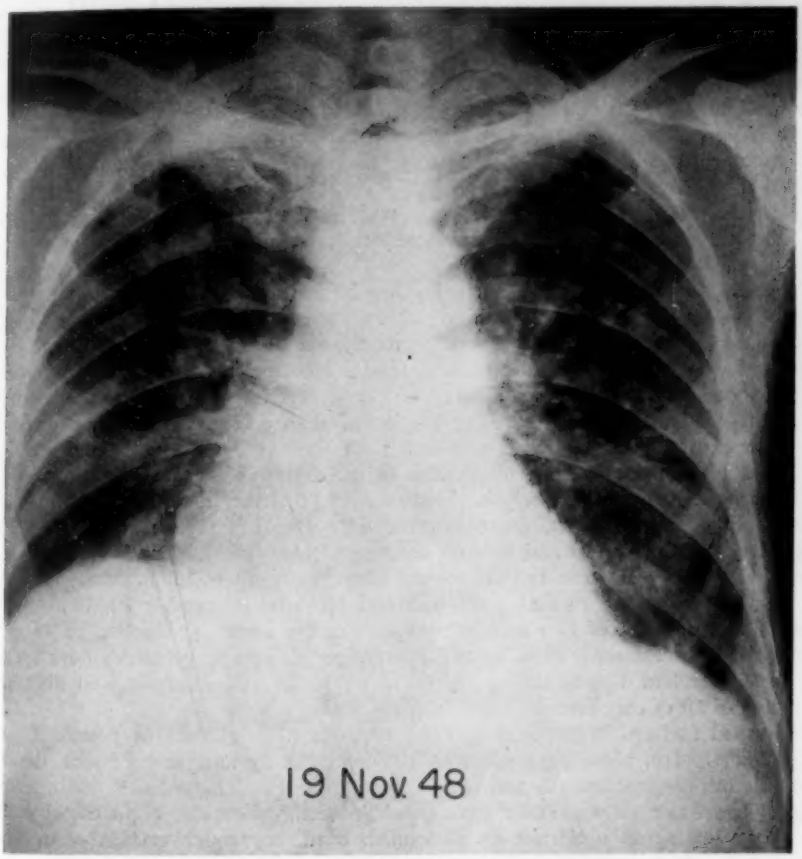

FIG. 7. *Case 5.* Roentgenogram of the chest taken six months after the previous film. This reveals a diffuse infiltration of all lobes, both lungs. The cardiac outline shows evidence of right ventricular dilatation.

Laboratory Data: Examination of sputum for tumor cells was negative April 7, 1948, and positive on July 30 and August 20, 1948. *Candida* species were cultured from specimens of sputa.

Significant autopsy findings:

Gross: Patient had a poorly differentiated primary bronchogenic adenocarcinoma which had metastasized to the right cerebral hemisphere, the left side of the pons,

the liver, mediastinal and para-aortic lymph nodes, the vertebrae and the pleura bilaterally. The left lower lobe was the primary site, since only here did tumor ulcerate through the mucosa of the bronchi (posterior basic), and here the tumor was greatest in amount and density. In all other respects the lungs were similar. The left lung weighed 1,285 gm., the right 1,720 gm. They did not collapse even on manipulation. Subpleural lymphatics were very prominent. Cut surfaces were fibrotic. Vessels and bronchi were unusually prominent.

Microscopic: (Lung description only.) All sections from all lobes were similar. Alveoli were filled and distended by sheets and nests of poorly differentiated cells, frequently containing vacuoles. Alveolar architecture usually persisted and was easily recognized. In addition, lymphatics everywhere, including subpleural lymphatics, were distended with tumor cells and this was associated with a fibrotic reaction. Blood vessels were thickened, some were obliterated, and a few contained tumor cells in their lumens (figure 5).

Only part of the respiratory embarrassment in this case was due to the pulmonary and vascular fibrosis. At least terminally, the intra-alveolar spread of tumor contributed to the dyspnea.

Case 5. A 61 year old white male was last admitted to Fitzsimons General Hospital on September 20, 1948. He was first treated at this hospital in 1921 and 1922 for pulmonary tuberculosis.

Present Illness: For the past two years he had had a gnawing mid-epigastric pain, which did not follow any specific pattern until one year ago. At that time, the epigastric, nonradiating pain occurred regularly one to one and a half hours before meals and was relieved by eating bland food. He developed dyspepsia, but denied vomiting, constipation, or bloody, tarry or clay-colored stools. He was admitted to Fitzsimons General Hospital on May 19, 1948, because of these symptoms. At this time he appeared well developed and well nourished and not acutely or chronically ill. A barium enema, a gastrointestinal series and a cholecystogram were interpreted as normal. Gastric analysis revealed achlorhydria (histamine test). A chest roentgenogram showed apical fibrosis on the right (figure 6). His symptoms largely disappeared in four weeks and he was discharged from the hospital with the recommendation that he return to the Outpatient Clinic at frequent intervals.

He was readmitted to Fitzsimons General Hospital September 20, 1948, because of exertional dyspnea of two months' duration and a cough productive of 45 c.c. of clear whitish, occasionally blood-tinged sputum per day of one month's duration.

His father had died at the age of 69 of pulmonary tuberculosis, and his mother at the age of 60 of carcinoma.

Physical findings in September, 1948, revealed a weight of 167 pounds (normal 182 pounds). His blood pressure was 104 mm. Hg systolic and 72 mm. diastolic, pulse rate 80, respirations 20, and temperature 98.6° F. The positive findings were: bilateral basal râles, a nontender liver palpable 1 cm. below the right costal margin, and in the left upper quadrant an ill-defined, hard, nontender mass, measuring approximately 4 by 6 cm., which did not move on respiration.

A chest roentgenogram taken in September, 1948, revealed a reticular, linear infiltration throughout both lung fields (figure 7). It was thought that this represented lymphatic permeation of carcinoma in the lungs.

Significant Laboratory Findings: Sputum cultures revealed *Candida* species. Sputum examination for tumor cells was negative. Stools were positive for occult blood on two occasions. Electrocardiograms obtained on October 8, 1948, and on November 1, 1948, showed no particular abnormalities. An electrocardiogram on November 19, 1948, revealed low voltage and right axis deviation. A repeat gastrointestinal series taken October 26, 1948, revealed a large filling defect in the prepylorus and in the pylorus.

Hospital Course: The patient's chief complaint was progressive shortness of breath up to his death. In October he started vomiting and had abdominal distention. His cough remained productive of about 60 c.c. daily. He remained afebrile throughout his hospitalization. November 19, 1948, his pulse became rapid and dyspnea increased. He died November 21, 1948.

FIG. 8. *Case 5.* Thrombosed large vessel (A), thickened small vessels (B), perivascular lymphatics filled with tumor (C), and generalized fibrosis.

Significant autopsy findings:

Gross: The right ventricle was slightly dilated and its myocardium measured 0.7 cm. in average thickness. The abdomen contained 4,200 c.c. of slightly cloudy amber fluid. Eighty per cent of the stomach was infiltrated by scirrhous adenocarcinoma. There were metastases to the first part of the duodenum, small and large intestine, regional lymph nodes, the liver, omentum, mesentery, left adrenal, pelvic peritoneum, vertebrae and all lobes of both lungs. There were 125 c.c. pericardial effusion, 1,000 c.c. right pleural effusion and 750 c.c. left pleural effusion.

The right lung weighed 675 gm., the left 625 gm. They did not collapse on opening the chest, were crepitant throughout, yet felt firmer than normal. Cut surfaces contained coarse fibrous trabeculations, but no grossly recognizable tumor metastases or tumor nodules. There was a healed tuberculous apical scar in the right lung. Pulmonary arteries contained minimal atherosclerotic changes.

Microscopic: (Lung description only.) All sections contained numerous nests of tumor cells in diffuse and haphazard distribution. They were found in distended subpleural lymphatics, in perivascular lymphatics, in some alveoli and in a few small blood vessels. The lymphatic involvement was most prominent and was associated

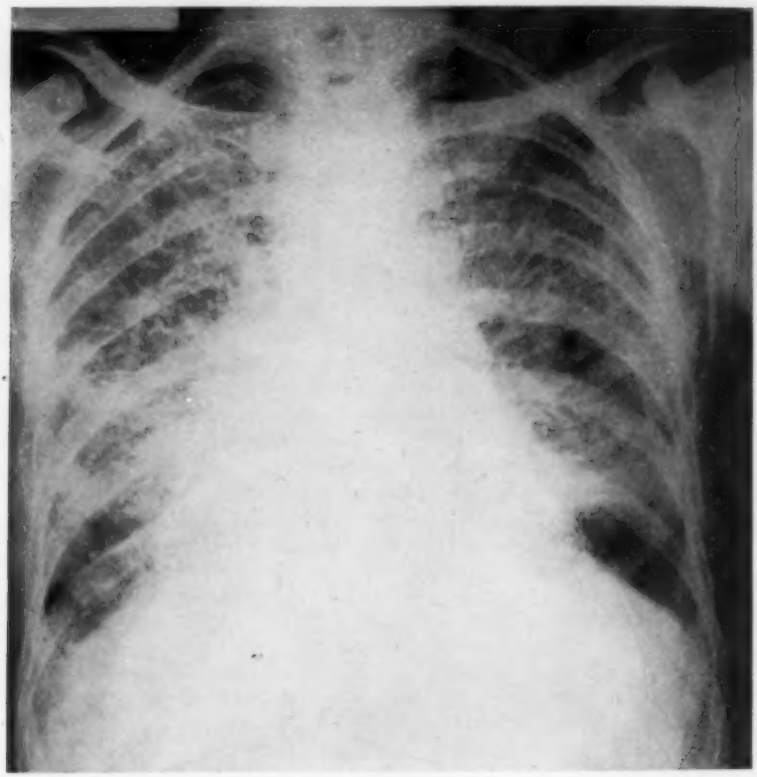

FIG. 9. *Case 6.* Roentgenogram of May 26, 1949, showing marked progression of the pulmonary infiltration with blunting of the right costophrenic angle.

with fibrosis of the surrounding tissue. In the case of perivascular lymphatics, the reaction involved the entire vessel wall, which then appeared considerably thickened. Some of the vessels showed considerable endothelial proliferation, some were completely occluded and some were thrombosed. Although considerable tumor was present, the degree of fibrosis appeared to be out of proportion to the amount of tumor (figure 8).

Case 6. A 71 year old white male was well until approximately April 1, 1949, when he developed a productive cough and noted the onset of mild orthopnea. One week later he became dyspneic and this became progressively more severe. He lost

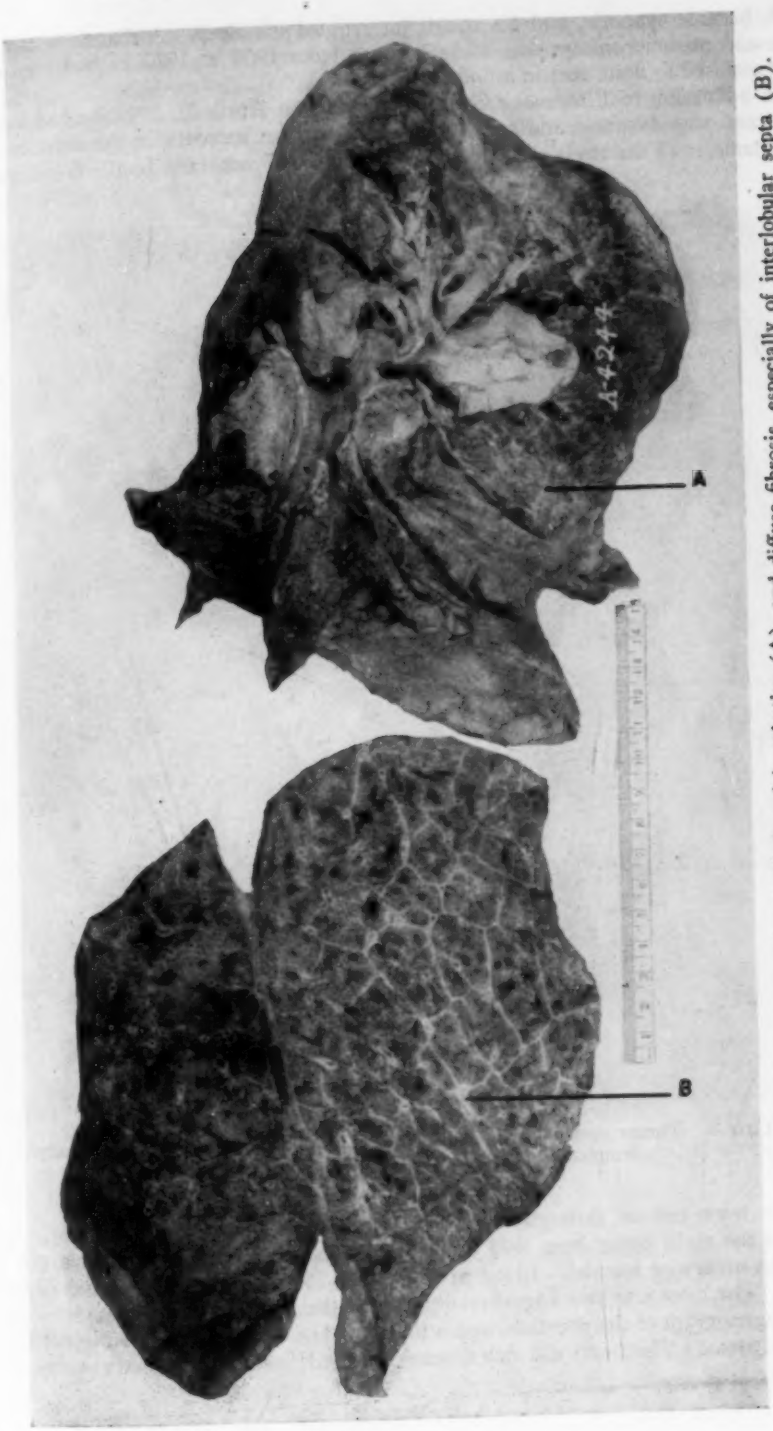

FIG. 10. *Case 6.* Left lung, showing prominent subpleural lymphatics (A), and diffuse fibrosis, especially of interlobular septa (B).

weight, became cyanotic, and his cough interrupted his sleep. A diagnosis of heart failure and pneumoconiosis was made because from 1908 to 1920 he had been constantly exposed to flour dust in a flour mill.

On admission to Fitzsimons General Hospital on April 29, 1949, he had lost 18 pounds and was dyspneic and cyanotic. There was an increase in the anterior-posterior diameter of the chest, with bilateral limitation of motion. Tactile fremitus and

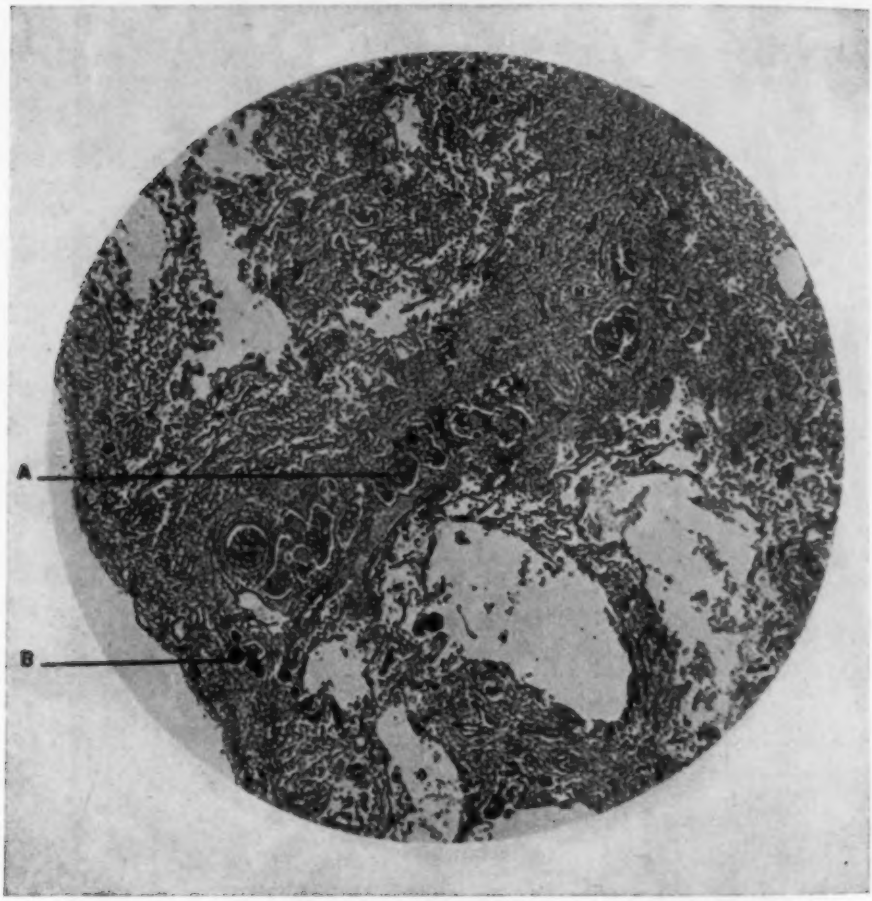

FIG. 11. *Case 6.* Tumor distending lymphatics of interlobular septum (A) and subpleural lymphatics (B). Diffuse fibrosis is present.

percussion were normal throughout. There were râles throughout the chest, most marked in the right upper lung field anteriorly. The heart was slightly enlarged to the left but otherwise normal. Blood pressure was 140 mm. Hg systolic and 72 mm. diastolic. The liver was two fingerbreadths below the right costal margin.

Roentgenogram of the chest showed a linear nodular infiltration fanning out from both hilar areas. The heart did not appear enlarged but the pulmonary conus was prominent.

The patient showed no response to antibiotic therapy and digitalization. His symptoms became progressively more severe. Two sputum smears showed numerous anaplastic tumor cells. Electrocardiogram on May 2, 1949 showed right axis shift. Roentgenogram on May 26, 1949 (figure 9) showed a definite and marked extension of the diffuse linear bilateral pulmonary infiltration. The patient died on May 29, 1949, one month after hospitalization and two months after the onset of his symptoms.

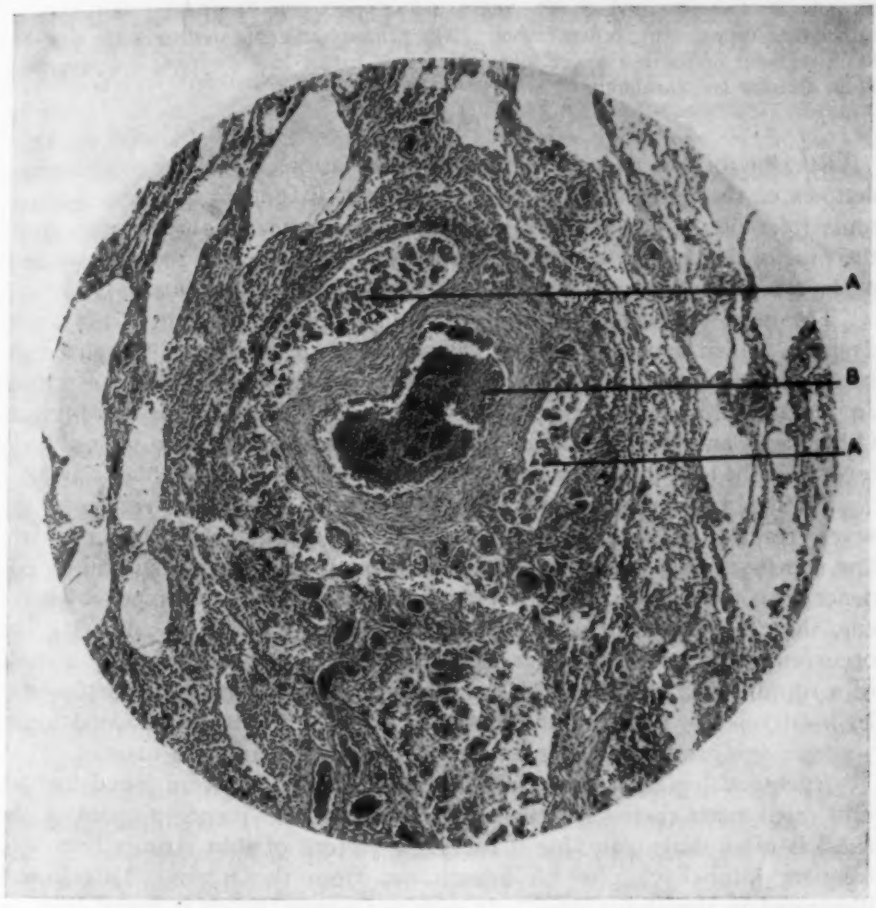

FIG. 12. *Case 6.* Tumor dilating perivascular lymphatics (A). Mural thrombus forming in a thickened artery (B).

Significant autopsy findings:

Gross: An intensive search was made for an extrapulmonary source for the malignancy but none could be found. There were small, obviously metastatic tumor nodules in the liver, adrenals and mediastinal lymph nodes and one mesenteric lymph node. There was moderate cardiac hypertrophy (395 gm.), with right ventricular dilatation and bilateral hydrothorax (right 1,300 c.c., left 1,400 c.c.) The right lung weighed 1,080 gm., the left 760 gm. Both were rather firm, retained their shape, and

were covered by thickened pleura with numerous prominent lymphatic markings. No primary tumor could be found in any bronchi, including those of the third and fourth order. Cut surfaces were grayish-tan, with prominent septal and linear fibrotic bands. No distinct nodules were present to suggest the point of origin of the tumor (figure 10).

Microscopic (figures 11 and 12): Tumor cells, distended alveoli and perivascular, septal and subpleural lymphatics everywhere. The tumor was associated with a moderate fibrosing reaction, a tendency to obliteration of small vessels and, in places, thrombosis of small arteries. The tumor cells appeared to be growing in lymphatics rather than representing tumor emboli. The primary site appeared to be the posterior basic segment of the left lower lobe. Here the tumor had the typical arrangement of an alveolar cell carcinoma.

Discussion

Because of the bizarre clinical manifestations, lymphangitic carcinomatosis of the lungs often presents a difficult diagnostic problem. Symptoms referable to the primary neoplasm are frequently absent, even up to the time of death. In other patients the symptoms due to the primary neoplasm are present but are masked by the pulmonary symptoms.

The most striking and constant finding in these patients is the severe dyspnea, which appears to be progressive and unrelenting. Cough occurs in about 60 per cent of these patients,[1] and is usually productive of only small amounts of white tenacious sputum, which may occasionally be blood-tinged. Other signs and symptoms are pleuritic-type chest pain, cyanosis, low grade fever, weight loss, anorexia and weakness.

Physical examination quite frequently fails to explain the reason for the severe respiratory symptoms. Examination of the lungs discloses relatively few signs—usually medium râles or occasionally sibilant râles, with no evidence of consolidation. If cor pulmonale and cardiac decompensation occur, there may be evidence of pleural effusion (cases 2, 4 and 6). The occurrence of a spontaneous pneumothorax in case 4 was probably a result of a rupture of a subpleural bleb associated with compensatory emphysema. In most reports, lymphangitic carcinomatosis of the lungs is found in the younger age group.[1, 2] This was not true in the above six cases.

Roentgenologic Picture: Only a few recent articles were found that are illustrated with roentgenograms.[2, 11] Actually, the roentgenogram of the chest is often diagnostic, for it reveals a pattern of thin stringy lines with frequent interweaving which branch out from the hilum. This is well illustrated in the above cases. If such a roentgenogram is found with the above-mentioned symptoms, and miliary tuberculosis, fungous diseases and occupational diseases are ruled out, lymphangitic carcinomatosis of the lung should be suspected. Of all sites, the stomach should be the first investigated.

Sputum examinations are often misleading, as in case 1 with a positive smear for acid-fast bacilli, and in cases 3, 4 and 5, in which *Candida* species were cultured. Sputum examination for tumor cells was positive in cases 4 and 6 (the first an instance of bronchogenic carcinoma and the second

of pulmonary alveolar cell carcinoma), but is usually negative in metastatic carcinoma to the lungs.

Electrocardiograms often reveal evidence of cor pulmonale, and this was found in three of the cases. In case 4, the electrocardiogram at onset of his illness revealed a left axis deviation, but six months later and two months before death the electrocardiogram showed a cor pulmonale pattern. In case 5 the electrocardiogram showed a cor pulmonale pattern two days before death. In case 6 the electrocardiogram showed a right axis shift.

The method of spread of the neoplasm to the lymphatics of the lungs is probably by retrograde lymphatic permeation,[6] with the tumor cells growing along lymphatic channels. In cases 2, 3 and 5 the spread occurred from a primary carcinoma of the stomach. It has been suggested that the tumor spreads along the paraesophageal lymphatics, thence through the hilar anastomoses into lung parenchyma as well as through a hematogenous route. It is interesting to note that the left lung in case 1, which had been collapsed by a thoracoplasty, failed to reveal any evidence of tumor infiltration. This may be related to the observation that in hematogenous miliary tuberculosis, a lung collapsed by thoracoplasty likewise escapes involvement.

The pathologic changes within the lung were described in Greenspan's excellent article.[12] He believed that secondary endarteritis was the most important factor responsible for the occurrence of right heart failure. He stated that as early as 1899 Girode described the finding of endarteritis in the pulmonary arteries in these cases of lymphangitic carcinomatosis of the lungs. However, the French authors were of the opinion that the respiratory symptoms were a direct result of invasion of the lymphatics by the neoplastic cells, causing a compression of the bronchioles and alveoli, and that the vascular changes were not the primary factor in causing the respiratory symptoms.

Spain [13] in 1946 mentioned that diffuse lymphatic carcinomatosis is the most common cause of subacute cor pulmonale. Schattenberg and Ryan [5] have described in detail the postmortem findings. Our patients consistently showed fibrosing perivascular, vascular and pulmonary changes associated with the lymphangitic spread of a degree sufficient to explain at least in part the clinical findings. It is believed that the pulmonary syndrome found in these patients is a result of all of these changes and that they are not found separately; when lymphangitic carcinomatosis of the lungs occurs, regardless of the primary site, a diffuse pulmonary fibrosis and an obliterative arteritis are always to be found and are the causes for the clinical findings.

Summary

1. Six cases of lymphangitic carcinomatosis of the lungs are presented, with the pathologic findings and a brief review of the available literature.

2. The absence or masking of symptoms referable to the primary neoplasm is emphasized.

3. The roentgenograms, laboratory and pathologic findings are discussed.

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PARKINSONISM AND RHEUMATOID ARTHRITIS*

By RALPH O. WALLERSTEIN, M.D., *Boston, Massachusetts*

EIGHTY years ago Charcot first called attention to the possible relationship between Parkinsonism and rheumatoid arthritis. Since then several investigators have pointed out similarities between the two diseases. Chronic atrophic arthritis following encephalitis lethargica has been reported by Lichtwitz and Grimaldi. Describing certain clinical features common to both diseases, Sicard advanced the hypothesis of common central cerebral origin.

In an effort to evaluate critically the relationship between the two diseases, 19 patients with frank clinical paralysis agitans, and 28 patients with far advanced, chronic atrophic arthritis were examined. All patients were inmates of the Laguna Honda Home for the aged of San Francisco County; they constituted all cases of Parkinsonism and rheumatoid arthritis in the hospital from April to July, 1949.

In most patients with Parkinsonism the onset of illness had been very gradual; weakness and tremor had been the first symptoms. Table 1 contains pertinent data on the patients examined.

TABLE I

	Parkinsonism	Rheumatoid Arthritis
Total cases	19	28
Male	16	6
Female	3	22
Age range	41–81	37–80
Average age	59.6	62
Age of onset	14–69	4–67
Average age of onset	48.2	42
Tremor (180–300/min.)	19	1
Parkinsonian mask	18	1
History of joint pain	1	28
Evidence of joint destruction (x-ray)	1	28

In conducting the examinations, attention was focused primarily on the joints. In the majority of the patients, the appearance of the hands bore a marked resemblance to the hands found in chronic rheumatoid arthritis. There was ulnar deviation of the wrists and fingers, flexion at the metacarpophalangeal joints, extension at the phalangeal joints and adduction of the fingers and thumb; in other words, all muscles innervated by the ulnar nerve seemed overactive. Poverty of motion of trunk and face, with attitude of flexion at elbows and knees, enhanced this resemblance. But whereas

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in atrophic arthritis there is a true loss of mobility, affecting passive as well as active motion and usually ankylosis and deformity, full range of motion could be obtained in the joints of patients with Parkinsonism after overcoming the muscular rigidity by passively flexing and stretching all the large and small joints of the extremities.

Table 2 shows the results of roentgen-ray examinations of the hands of the patients with Parkinsonism. On assuming a new position, the hands lost their tremor for 15 to 45 seconds, long enough to obtain good pictures. Only one patient, a 63 year old woman, showed typical lesions of atrophic arthritis with joint destruction and ankylosis. All others showed varying degrees of periarticular demineralization and slight thinning of the joint spaces. These changes did not differ significantly from the roentgenographic changes of other old, inactive patients and patients with flaccid paralyses.

TABLE II

X-Ray Findings in Patients with Parkinsonism

Periarticular demineralization	10
Narrowing of phalangeal joint space	9
Localized bone destruction	1
Joint deformity	1
No demonstrable pathology	7

The patients suffering from rheumatoid arthritis had a definite story of onset with fever and joint pain. In all patients the disease had progressed to complete crippling, with joint destruction and ankylosis. Table 1 shows a comparison of the two groups of patients.

Only the patient referred to above appeared to have the characteristics of both diseases. She had suffered her first attack of joint pain and fever at the age of 31. Deformities and ankylosis were fully developed when the first tremors of paralysis agitans appeared at the age of 56.

SUMMARY AND CONCLUSION

1. Nineteen patients with Parkinsonism were examined for clinical and roentgenographic evidence of rheumatoid arthritis.

2. Certain superficial similarities of the hands were noted.

3. Absence of true joint disease by clinical or roentgenographic evidence was demonstrated in patients with Parkinsonism.

4. Only one patient appeared to have both diseases. In view of the number of cases of Parkinsonism (19) and rheumatoid arthritis (28) among a group of 500 patients, this coincidence cannot be considered significant.

5. There appears to be no increased incidence of rheumatoid arthritis among patients suffering from Parkinsonism.

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PROGNOSIS IN IDIOPATHIC THOMBOPHLEBITIS*

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Thrombophlebitis is recognized not only as a syndrome per se, but also as a signal that some basic pathologic state may exist elsewhere in the body of the person afflicted. That an episode of thrombophlebitis may be associated with some systemic illness has been stressed by Trousseau,[1] Cooper and Barker,[2] Barker,[3] and Thompson.[4] Cooper and Barker and Thompson have emphasized the association of thrombophlebitis with malignant tumors. It has been stated that carcinoma of the pancreas is particularly prone to be related with episodes of thrombophlebitis. However, malignant tumors of the pelvis, retroperitoneal space, stomach, lung and breast also have been said to be associated with episodes of thrombophlebitis. Inasmuch as the malignant tumors of these tissues are those most frequently encountered, it may simply denote an association of thrombophlebitis with any type of malignant disease.

Other systemic diseases known to have, at times, thrombophlebitis as a part of their course include thromboangiitis obliterans, blood dyscrasias such as polycythemia vera, leukemias, or any type of anemia, and heart disease such as cardiac decompensation or myocardial infarction. Any infectious disease may predispose to thrombophlebitis. The occurrence of the latter in the postoperative or postpartum state is well known. Local disturbances such as trauma, intravenous infusions or localized infections may result in thrombophlebitis due to direct involvement of a vein.

After all these situations have been considered, however, there remains a group of patients in whom thrombophlebitis develops without apparent cause. For lack of a better understanding of the abnormal physiology involved, these patients are said to have idiopathic thrombophlebitis. This may occur in single or multiple episodes and, if the latter, the term "recurrent idiopathic thrombophlebitis" is used. The term "thrombophlebitis migrans" has also been used to designate these recurrent episodes. Briggs,[5] Barker[6] and Fischer[7] have written about this problem. However, most of the case reports discussed by them have not taken into consideration the element of time as it pertains to the course of the syndrome. Most of the patients were followed for relatively short periods of time. The purpose of our study was to determine the prognosis for a group of patients who had had idiopathic thrombophlebitis, single or recurrent, for at least five years.

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Methods and Material

Retrograde from December 31, 1942, data on 120 consecutive cases in which the diagnosis of idiopathic thrombophlebitis was made were collected from the files of the Mayo Clinic. Fourteen hundred twenty-five cases of thrombophlebitis of all types occurred during the period in which the cases of idiopathic disease were encountered. The 120 cases represented 8 per cent of the total. In each instance the diagnosis of idiopathic thrombophlebitis had been made by one of the consultants in the Division of Medicine specializing in the study of peripheral vascular diseases. An attempt was made to obtain information from patients with idiopathic thrombophlebitis in whom the original episode of thrombophlebitis had occurred at least five years previously. In 22 instances the patients were seen at the clinic five or more years after the original diagnosis had been made. In the remaining 98 cases correspondence was directed to each patient. In 32 of these 98 cases no information could be obtained; however, adequate information was obtained in 66 of these cases which, combined with the 22 in which the patient was seen at the clinic, gave a total of 88 cases for study.

With material made available from case records and letters, an attempt was made to determine the following in each case: (1) recurrent episodes of thrombophlebitis; (2) development of chronic venous insufficiency; (3) development of chronic occlusive arterial disease; (4) occurrence of pulmonary embolism; (5) death and cause of death; (6) subsequent development of diseases which might have a relationship to thrombophlebitis, and (7) effect of use of tobacco on recurrences of thrombophlebitis.

Results

The 88 cases were arbitrarily divided into two groups. There were 29 patients (33 per cent) in whom only one attack of thrombophlebitis had occurred by the time they were first seen at the clinic. There were 59 patients (67 per cent) in whom multiple episodes of thrombophlebitis had occurred by the time they were first seen.

Twenty-Nine Patients with a Single Episode of Thrombophlebitis. Age When First Seen at the Clinic: This ranged from 15 to 76 years.

Sex: There were 21 males (72 per cent) and eight females (28 per cent).

Site of Lesion: Six patients (21 per cent) had superficial thrombophlebitis alone. Five patients (17 per cent) had both deep and superficial veins involved. Eighteen patients (62 per cent) had only deep veins involved. No females exhibited superficial thrombophlebitis alone, but five females had episodes with *both* deep and superficial veins involved. Thrombophlebitis involving the upper extremity did not occur.

Recurrences of Thrombophlebitis: Two patients (7 per cent) experienced recurrences; both were males who originally had had deep thrombophlebitis.

Chronic Venous Insufficiency: In 13 patients (45 per cent) chronic venous insufficiency developed. Ten of these patients had had only deep

thrombophlebitis. Three had had both deep and superficial thrombophlebitis.

Pulmonary Embolism: Nine patients (31 per cent) had episodes of pulmonary embolism. Eight of these patients had had only deep thrombophlebitis; one had had superficial thrombophlebitis only.

Mesenteric Thrombosis: This did not occur in this group.

Patients Subsequently Asymptomatic: Eleven (38 per cent) of the 29 patients had no ill health of any type after they were dismissed from the clinic.

Deaths: One patient died of carcinoma of the breast seven years after her only attack of thrombophlebitis. Another patient died of an unknown cause within 24 hours of the onset of a subsequent episode of thrombophlebitis which occurred three months after she had left the clinic.

Subsequent Development of a Disease Which Might Sometime in Its Course Be Associated with Thrombophlebitis: The one patient who might fall into this group was the one in whom carcinoma of the breast developed. The diagnosis of the tumor was not made until seven years after the single attack of thrombophlebitis. In none of the other 28 patients did a disease develop which might have a relationship to thrombophlebitis for the period of time covered by our follow-up study.

Fifty-nine Patients with Multiple Episodes of Thrombophlebitis. Age When First Seen at the Clinic: This ranged from 15 to 75 years.

Sex: There were 58 males (98 per cent) and one female (2 per cent).

Site of Lesions: Fifteen patients (25 per cent) had had repeated instances of superficial thrombophlebitis alone before examination at the clinic. Sixteen patients (27 per cent) had had episodes of deep thrombophlebitis only. Twenty-eight patients (47 per cent) had had both deep and superficial veins involved. Thrombophlebitis of the veins of the upper extremities had occurred in 10 patients (17 per cent) in addition to the thrombophlebitis of the lower extremities.

Recurrences of Thrombophlebitis: Twenty-five patients (42 per cent) suffered from subsequent recurrences and these were all males. Eighteen of these 25 patients had thrombophlebitis of both deep and superficial veins. In six, only superficial veins were involved, and in one, only deep veins.

Chronic Venous Insufficiency: In 45 patients (76 per cent) chronic venous insufficiency developed. This occurred in 25 patients (42 per cent) who had had involvement of both deep and superficial veins. It occurred in 15 patients (25 per cent) who had had only deep veins involved, and in only five (8 per cent) with thrombophlebitis confined to superficial veins.

Pulmonary Embolism: Twenty-three patients (39 per cent) had episodes of pulmonary embolism. This occurred in 13 patients with both deep and superficial thrombophlebitis. It occurred in seven with only deep veins involved, and in three with only superficial veins involved.

Mesenteric Thrombosis: Two male patients (3 per cent) who had had

both deep and superficial thrombophlebitis subsequently experienced mesenteric thrombosis.

Patients Subsequently Asymptomatic: Six patients (10 per cent) did not have further difficulty after their investigation.

Deaths: A total of 13 deaths occurred within three months to nine years after the date of initial examination at the clinic. Mesenteric thrombosis resulted in one death nine years after initial examination. Three patients died after "heart attacks" one to three years later; the exact nature of the "heart attacks" was not determined. One patient died of unknown cause after a herniorrhaphy performed three months after examination at the clinic, and two deaths resulted from cerebrovascular accidents after one and two years, respectively. One patient died from carcinoma of the lung nine months after examination, and another died from carcinoma of the colon three months later. One death was caused by abdominal malignancy four years after the patient was seen at the clinic; the exact nature of this malignancy was not determined. In three instances death occurred four to five years after examination, and the cause of death was not determined in these cases.

Subsequent "Etiologic" Diagnoses: Eight patients (14 per cent) subsequently had diseases which may have been related to the development of thrombophlebitis. These conditions were not diagnosed at the time of the patients' initial examination at the clinic, but were discovered at a later date. One chondrosarcoma of the larynx became manifest two years after the original examination at the clinic. One carcinoma of the lung was discovered several months later, and one carcinoma of the colon was diagnosed three months later. One patient was found to have Hodgkin's disease two years later. One carcinoma of unknown origin occurred in the abdomen four years after the initial examination at the clinic. In one case polycythemia vera developed eight years later. Two patients were found to have thromboangiitis obliterans with arterial involvement three and four years later, respectively.

Patients Subsequently Asymptomatic as Determined by Inquiry: Of the 59 patients in this group, only six (10 per cent) had no such additional symptoms in the ensuing five years. Five of these six patients were in the group afflicted only by thrombophlebitis of the superficial veins.

Effect of Use of Tobacco: Sufficient information was obtained in 73 cases to allow limited study of the effect of tobacco on recurrences of thrombophlebitis. In the group of patients with only a single episode of thrombophlebitis prior to examination at the clinic, there were 12 persons who used tobacco and 14 who did not. There was a recurrence of thrombophlebitis in one patient in each of these two groups. Interestingly enough, the recurrence in the group known to use tobacco came in the only individual known to have stopped smoking.

In the group of patients who had had multiple episodes of thrombo-

phlebitis at the time of the initial examination, there were 38 persons who used tobacco and nine who did not. There were recurrences of thrombophlebitis in 18 persons (46 per cent) of the group which used tobacco. There was one recurrence (11 per cent) of thrombophlebitis in the group which did not use tobacco. Of 11 persons who said they had discontinued use of tobacco, thrombophlebitis recurred in eight (73 per cent). In the 27 individuals who used tobacco and who did not discontinue its use, there were 10 recurrences (37 per cent). Any patient in whom there subsequently developed a disease which might have been etiologically related to the thrombophlebitis was excluded from this phase of the study.

Comment

Most of the findings in this study are in accord with the usual clinical opinions (Allen, Barker and Hines [6]). It is interesting that only a few patients subsequently had a serious illness which might be related to the occurrence of thrombophlebitis. There were only two instances of subsequent development of abdominal malignancy in the entire series. There is a possible source of error in the study because of failure to get information on 32 patients of the original group. A significant number of this group may have died, and this might account for the few subsequent "related" diseases which were discovered following the original diagnosis of idiopathic thrombophlebitis.

In a follow-up study by letter, answers should be received from patients who are living and well and who were satisfied with their care. In the 32 cases in which no information was obtained, over 90 per cent of the letters were returned by the post office as unclaimed. This problem is imponderable: Did the patient move to a new address or did he die? In any event the factor is recognized by us. We do not intend that the data presented be interpreted as complete and without some element of statistical error. Where percentages are used it is for convenience in comparison of the two groups in the study.

The predominance of males in this study is definite. This is particularly true in the group of patients suffering from recurrent idiopathic thrombophlebitis. Table 1 shows the sex incidence in idiopathic thrombophlebitis.

Table I

Sex Incidence in Idiopathic Thrombophlebitis

Thrombophlebitis	Patients				
	Total	Males		Females	
		No.	Per Cent	No.	Per Cent
Single episode	29	21	72	8	28
Multiple episodes	59	58	98	1	2

A number of patients who had been said to have idiopathic thrombophlebitis seemed to get along fairly well. In many of these patients (97 per cent of those with a single episode of thrombophlebitis prior to examination at the clinic and 86 per cent of those with multiple episodes prior to initial examination), a significant disease did not develop within the time limits of the study (five years and longer). Therefore, the term "idiopathic thrombophlebitis" may be used until the specific nature of the syndrome becomes apparent.

Recurrent thrombophlebitis may be a manifestation of thromboangiitis obliterans (Barker [6]). It is surprising to find that in only two patients did evidence of thromboangiitis develop. Both of these patients had experienced deep and superficial thrombophlebitis by the time of initial examination. From this information it might be assumed that most patients with *thromboangiitis obliterans* should be expected to demonstrate arterial involvement at the time when they first present themselves for examination for consideration of recurrent thrombophlebitis. Indeed, this may be true, for many patients with thromboangiitis obliterans are first seen because of recurrent thrombophlebitis. The determination of the presence of a chronic, occlusive arterial disease such as thromboangiitis obliterans by a questionnaire is by no means accurate, and it is well within the realm of possibility that such a condition could have developed in several persons without their knowledge. Therefore, we prefer to state only that in at least two patients, and perhaps more, thromboangiitis obliterans developed.

In five patients a malignant tumor is known to have developed. In one of these, carcinoma of the breast was detected seven years after a single episode of thrombophlebitis. With such a long interval of time it is impossible to know if a relationship existed between the thrombophlebitis and the carcinoma of the breast, but such a relationship probably did not exist in this instance. In addition to the subsequent development of five malignant tumors there was one patient who subsequently had Hodgkin's disease. Due to the awareness of the association of malignant tumors and thrombophlebitis, an extensive investigation for neoplasms is carried out by clinic physicians whenever confronted by a patient with an apparently "idiopathic" thrombophlebitis. By this procedure numerous neoplasms are detected and an "idiopathic" diagnosis is averted. We feel that this accounts, at least in part, for the relatively few *known* neoplasms which occurred subsequently. Therefore, it would seem that malignant tumors associated with thrombophlebitis are usually of such magnitude that they may be detected by proper investigation. The factor of the untraced patients, however, again must temper this consideration.

Reëxamination of the history of the patient who subsequently had a diagnosis of polycythemia vera revealed suggestively elevated erythrocyte counts at the time of initial examination. Therefore, it is advisable to consider the possibility of polycythemia vera in all cases in which there is thrombophlebitis for which there is no apparent cause.

TABLE II

Comparison of the Two Groups of Cases of Idiopathic Thrombophlebitis

	Single Episode	Multiple Episodes
Recurrence of thrombophlebitis, per cent	7	42
Subsequent chronic venous insufficiency, per cent	45	76
Pulmonary embolism, per cent	31	39
Patients subsequently asymptomatic, per cent	38	10
Deaths, per cent	7	22
Development of systemic illness, per cent	3	14

In this series of 88 patients, complications such as chronic venous insufficiency and pulmonary embolism occurred in a relatively large number of cases. The former was found to occur more frequently in the group of patients who had multiple episodes of thrombophlebitis. The two cases of mesenteric thrombosis also occurred in this group in which thrombophlebitis recurred.

The development of chronic venous insufficiency in such a large proportion of patients warrants comment. The use of appropriate elastic support as soon as the patient becomes ambulatory after the acute thrombophlebitis has subsided will almost always prevent indurated cellulitis, ulceration, and extensive pigmentation. Also, appropriate obliterative therapy of varicose veins may be necessary should the superficial veins be or become incompetent.

The incidence of pulmonary embolism is considerable in both groups of patients, yet no patient in this series is known to have died from this condition—a striking situation when one considers the possibility for fatalities in persons having pulmonary emboli. There is no significant difference in the incidence of pulmonary embolism in the two groups of patients (table 2).

Because some physicians have considered idiopathic thrombophlebitis to be related to thromboangiitis obliterans, many patients with the former syndrome have been advised to discontinue the use of tobacco (Harkavy[9]). In our series, the recurrences of thrombophlebitis in the group of tobacco-using patients who discontinued the use of tobacco were no less than in

TABLE III

Recurrences of Thrombophlebitis in Patients Who Used Tobacco

Thrombophlebitis	Patients				
	Total	Continued Use of Tobacco		Discontinued Use of Tobacco	
		Total	Recurrence	Total	Recurrence
Single episode	12	11	0	1	1
Multiple episodes	38	27	10 (37%)	11	8 (73%)

those who continued to smoke. The number of patients studied from this aspect was small, and the information from the patients who claimed to have stopped smoking may not have been entirely correct. There may have been a tendency for some patients to conceal the fact that they had continued to use tobacco in spite of their physician's advice to the contrary.

In the group of patients with single episodes of thrombophlebitis, recurrences developed in one patient in each of the smoking and nonsmoking divisions. It seems in the single-episode type of this syndrome that tobacco is not a factor in causing the original or subsequent thrombophlebitis. However, in the analysis of the group with recurrent thrombophlebitis, some questions may still be raised as to the possible etiologic rôle of tobacco in this syndrome. The use of tobacco was not associated with a higher incidence of recurrences of thrombophlebitis in smokers. It should be noted, though, that of nine nonusers of tobacco who had had multiple episodes of thrombophlebitis before their examination at the clinic, only one (11 per cent) subsequently had another episode. Eighteen of 38 smokers (47 per cent) with

TABLE IV

Recurrences of Thrombophlebitis in Patients Who Were Not Users of Tobacco

Thrombophlebitis	Patients	
	Total	Recurrences
Single episode	14	1 (7%)
Multiple episodes	9	1 (11%)

multiple episodes subsequently experienced recurrences. Thus, subsequent recurrences of thrombophlebitis seem to be more frequent in the group of persons who have, at one time or another, used tobacco. Our studies suggest this but do not prove it and, until more definite information is obtained relative to the rôle of tobacco in recurrent thrombophlebitis, an open mind to the problem should be maintained. The data on this aspect of the study are summarized in tables 3 and 4.

SUMMARY AND CONCLUSIONS

1. By means of a review of case records and follow-up letters, 88 cases of idiopathic thrombophlebitis have been studied for a period of five or more years from the time of initial examination and diagnosis.

2. Twenty-nine patients (33 per cent) had had only a single episode of thrombophlebitis prior to the time of initial diagnosis of idiopathic thrombophlebitis. Fifty-nine patients (67 per cent) had had multiple episodes prior to the time of initial diagnosis.

3. The complications, chronic venous insufficiency and pulmonary embolism, occurred in a relatively large number of patients. A greater incidence of the former occurred in those patients with multiple episodes of thrombophlebitis.

4. Death from a thrombo-embolic episode occurred in one case (mesenteric thrombosis). In seven other cases there exists the possibility that a fatal thrombo-embolic episode may have occurred. Sufficient information was lacking to make certain of the diagnosis in these cases.

5. Nine patients (10 per cent) subsequently had clinical evidence of a systemic disease which may have been an etiologic factor in the development of the thrombophlebitis. Malignant tumors developed in five patients. Hodgkin's disease developed in one patient, polycythemia vera in one, and thromboangiitis obliterans in two.

6. Idiopathic thrombophlebitis occurs predominantly in the male. There were only nine females (10 per cent) in the entire group of 88 cases. Only one female patient (1 per cent) had recurrent thrombophlebitis.

7. Eleven (38 per cent) of the 29 patients with a single episode of thrombophlebitis were asymptomatic in the ensuing five years. Six (10 per cent) of the 59 patients with multiple episodes of thrombophlebitis likewise had no further trouble.

8. Discontinuance of the use of tobacco seemed to have little effect in preventing recurrences of thrombophlebitis.

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DIENCEPHALIC EPILEPSY AND THE DIENCEPHALIC SYNDROME *

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HARVEY CUSHING,[1] in his discussion of diencephalic-hypophyseal symptomatology, stated: "Here in this well-concealed spot, almost to be covered by a thumb nail, lies the very mainspring of primitive existence—vegetative, emotional, reproductive—on which, with more or less success, man has come to superimpose a cortex of inhibitions. The symptoms that arise from disturbances of this ancestral apparatus are beginning to stand out in their true significance. . . .

"The diencephalo-hypophyseal mechanism can only be properly interpreted when looked upon as a whole. The active principle of the neurohypophysis is in part excreted into the blood stream and in part into the cerebrospinal fluid. The former causes pallor from vasoconstriction and stimulates the musculature of the lower bowel; when introduced into the human ventricular system, it causes flushing, sweating, salivation, lacrimation, vomiting and pronounced fall in body temperature. The former bears resemblance to a sympathetic effect; the latter appears to be essentially a cranial autonomic or a parasympathetic effect. . . .

"Under emotional stimuli the posterior lobe is discharged through the tubero-hypophyseal fibre paths, portions of the active principle acting on the diencephalic nuclei controlling the parasympathetic apparatus. Conditions may arise where sufficient posterior pituitary secretion is discharged to call forth a parasympathetic response as diffuse as that brought about by discharge of adrenalin on the sympathetic system. The neurohypophysis, in short, may be related to the parasympathetic system, as the adrenal medulla is related to the sympathetic division of the vegetative nervous system."

Exclusively autonomic epileptic seizures do occur without any evidence of primary somatic or physical involvement, although they are rather rare. (This argues strongly for special representation of visceral functions.) The inclusion of various visceral manifestations in epileptic seizures is a frequent and almost universal phenomenon. These visceral seizures may be separated into visceromotor and viscerosensory components.

Penfield [2] described a case of diencephalic epilepsy. This occurred in a woman of 41 and was due to a tumor causing pressure over the third ventricle. She suffered numerous attacks characterized by periodic headaches and occasional loss of consciousness. A typical attack lasted about 10

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minutes. The face became flushed and profuse diaphoresis was noted. Breathing was rapid at the onset, becoming Cheyne-Stokes in character. The pulse, full at the onset, became weaker and slower as the attack progressed. Salivation and lacrimation were noted. The eyes appeared to be protruding. Attacks of shivering were frequent, followed by sudden vasodilatation of the skin. There were sudden rises in blood pressure. The pupils were contracted or dilated. The blood pressure ranged from 122/75 to 200/100 mm. of mercury. Pilomotor disturbance with the appearance of "goose flesh" was noted. The temperature was below normal.

We are reporting a case of diencephalic epilepsy following mumps encephalitis. The case is reported in detail because of its rarity, the embodiment of diverse autonomic patterns, and the effectiveness of estrogenic hormones in the control of the seizures.

Case Report

Case 1. The patient was 39 years old when her present illness began. Her past personal history was not remarkable. She was married in 1933; a year later placenta previa complicated her pregnancy and a stillborn child was delivered. A second pregnancy in 1937 was uncomplicated.

In May, 1941, she contracted mumps from her son. The course was rather severe, with high fever and painful parotids. On the seventh day of illness, she developed intense headaches, weakness and tremulousness. On the next day, an insatiable thirst developed; she drank quarts of water and passed large quantities of urine of low specific gravity. Many urine examinations failed to show sugar; a blood sugar that day was reported as 78 mg. per cent.

Diabetes insipidus and encephalitis were diagnosed. One-half cubic centimeter of pituitrin was injected every two hours for seven doses on the ninth day of her illness. Similar frequent doses had to be continued for the next two days. The following four days 1 c.c. at four-hour intervals controlled the diuresis. During the next 10 days, she got along with injections of 1 c.c. morning and night. For the next four weeks there was no need for pituitrin, except during the first two days of her menses, at which time recurrence of diuresis and thirst was controlled by a single injection of 1 c.c. of pituitrin.

The fever gradually abated after the twelfth day. Headaches and weakness persisted for several weeks. At no time was the blood pressure elevated. The heart was regular and of good tone.

With the onset of diabetes insipidus she complained of frequent attacks of intense abdominal colic, accompanied daily by diarrhea. There was involuntary spasm all over the abdomen, and tenderness was noted over the epigastrium and both iliac fossae. On the twelfth day of her illness, intense uterine colic and menorrhagia began and continued for four days and added to her exhaustion.

As the need for pituitrin abated, the headaches, weakness, abdominal colic and diarrhea waned.

Eight weeks following the onset of her encephalitis, she developed sharp colic with her menses. Symptoms of diabetes insipidus reappeared. She became acutely ill and complained of pounding headaches and a sense of constriction over her chest. The heart was noted to be irregular because of many premature contractions, and the blood pressure ranged from 110/70 to 170/110 mm. of mercury. A feeling of im-

pending syncope continued for hours. Abdominal colic and diarrhea added to her misery. The diuresis was controlled by injections of 1 c.c. of pituitrin at four-hour intervals. Trasentine and phenobarbital gave some relief from the abdominal cramps.

The next day she appeared exhausted. The very sight of food or drink would initiate a "constriction in her throat." A gurgling, choking sound would follow, climaxed by a piercing scream. Her eyes bulged and her face took on the appearance of rage. Her skin at one time would have a dry, pale, "goose flesh," leathery and cold quality; at other times it was warm, moist and flushed. The skin variations were not symmetrical. At times she had difficulty in breathing and became cyanotic. However, the flow of oxygen, given by mask, by nasal catheter or by tent, initiated repeated spasms and could not be continued. Her temperature fluctuated from 97.2° to 100.8° F.

Morphine, bromides, dilantin sodium and barbiturates proved ineffective. Periods of relaxation occurred only when she became so exhausted that one despaired of her life. After four days the attacks became less severe, abdominal colic and diarrhea subsided, and she began to ingest food and fluids. It required a month for her to recover her health.

With the onset of the following three menses there was need for pituitrin on the first day. The initial 48 hours of her menstrual periods were marked by abdominal cramps and diarrhea; dysmenorrhea and menorrhagia proved exhausting. A treatment program of trasentine and phenobarbital twice daily, and injections of progynon-B, 10,000 international units twice weekly, was established.

She got along very well with the ensuing menses. The trasentine was discontinued; the progynon-B injections were continued twice weekly. During the fall of 1941, and continuing until June, 1942, she continued with bi-weekly injections of 10,000 international units of progynon-B. She looked well and had no complaints. The menstrual periods were regular; there was no dysmenorrhea or menorrhagia. After June, 1942, she received a weekly injection of 10,000 international units of progynon-B. In 1944 and 1945 the injections were given every two weeks.

The patient decided to discontinue the injections in March, 1946. She did well until May, when her menses again became heavy and moderate diuresis was noted. With the menses in June, 0.5 c.c. of pituitrin was required to control the thirst and diuresis.

On July 10, 1946, with the onset of her menses, there recurred a major diencephalic episode. Abdominal colic, diarrhea, thirst, diuresis and extreme exhaustion occurred within a few hours. The sight of food or drink again initiated the "constriction of her throat," followed by a piercing scream, the appearance of rage and a severe constricting pain over the chest. The blood pressure reached 200/100 mm. of mercury. There were many premature cardiac contractions. Occasionally the pharyngeal muscle spasm was accompanied by cyanosis. Attempts at giving oxygen again seemed to precipitate further attacks. Variations in the appearance of the skin were as previously noted. Occasionally, irregular tremors were present in the extremities. Again morphine, barbiturates, dilantin sodium, tridione and bromides proved of no avail. Only the approach of syncope would lead to a remission of an hour or two. The diuresis was controlled by pituitrin. An occasional urine specimen revealed sugar. The temperature ranged from 97° to 101.2° F.

On July 14, the constriction over the patient's chest became unbearable and she expressed a feeling of impending death. The electrocardiogram was not remarkable except for premature contractions of ventricular origin. The "constriction in her throat" made it increasingly more difficult for her to breathe. A striking, livid cyanosis appeared. Her face again expressed rage and the eyeballs bulged. This

was followed by a series of piercing screams. Coarse tremors were noted over the body and extremities. The alterations of skin color and temperature appeared in waves. The temperature rose from 97.2° to 101.2° F.; the pulse was irregular; the blood pressure was variable, reaching as high as 200/110 mm. of mercury. There was a heavy trace of sugar in the urine. The fine tremors were repeated every few minutes and exhaustion was extreme.

At this time, libido became a prominent subjective symptom. She later described her sensations as follows: "I felt I was about to die. If I had had enough strength, I would have committed suicide; yet I had a constant desire to be with my husband." Vaginal burning and a thin vaginal discharge continued for the next few days. Again, all sedation proved ineffective.

On July 16, after six days of diencephalic status epilepticus, the symptoms began to abate. Two days later she was admitted to the Jewish Hospital of Brooklyn for intensive study during her remission. The following studies were carried out and all proved normal: roentgenograms of the skull, chest and gastrointestinal tract; intravenous pyelogram; electroencephalogram; glucose tolerance; spinal tap; electrocardiogram. Blood chemistry studies showed: calcium, 9.8 mg. per cent; phosphorus, 3.6 mg. per cent; phosphatase, 3.6 Bodansky units; cholesterol, 215 mg. per cent, of which 45.3 per cent was present as esters; sugar, 95 mg. per cent; urea nitrogen, 13.5 mg. per cent. A basal metabolism was done and reported plus 8. Many samples of urine were studied and found normal. The hemoglobin was 90 per cent; red blood cells, 4,310,000; white blood cells, 11,500, with a normal differential count. The patient remained in the hospital until August 1. There were no attacks during the period of hospitalization.

On August 4 menses occurred, and the next day the flow became heavy and the patient suffered a major recurrence. Despite all sedation, the attacks continued as previously described, with periods of quiescence only after collapse seemed imminent. Libido was again prominent. Because of the associated menorrhagia and uterine colic, progynon-B was given, 10,000 international units three times daily beginning on August 6. On August 10 there was an appreciable decrease in the intensity of the seizures. From August 11 to August 21 she received 50,000 international units daily. Injections of pituitrin were not needed after the third day of estrogenic hormone therapy. From August 22 until October 1, 10,000 international units twice daily were given. There were no further symptoms of diencephalic dysfunction after August 14. Because of inanition and weakness, parenteral vitamin B complex was given during August and September. No other medication was used.

She improved steadily and gradually regained her strength. From October 1 until November 1 she received 10,000 international units daily. From November 1, 1946, until June, 1947, she received 10,000 international units twice weekly. After July, 1947, and until March, 1948, 10,000 international units weekly were given. During this period of estrogenic therapy her menses was regular, not excessive, and lasted two or three days. Her general health was quite satisfactory.

In September, 1948, she embarked on a motor trip across country. It was decided to discontinue further estrogenic injections. (She carried with her, however, a generous supply.) Up to the time of this report there has been no recurrence.

This case embodies many of the features of Penfield's [2] case of diencephalic epilepsy. The wide range of emotional features, the vasomotor phenomena and the autonomic functional disorders characterize the syndrome. The rarity of this condition does not preclude its importance. Estrogenic hormone therapy in large doses proved to be the only effective remedy.

The Diencephalic Syndrome

The diencephalic syndrome is fairly common. It was originally described by Page [3] as the "hypertensive diencephalic syndrome." The syndrome was described "as occurring usually in young and middle-aged women, although it may be seen occasionally in men. It is characterized by hypertension of the labile sort, more especially by the periodic appearance of a blotchy blush which extends over the face and upper chest, seldom, if ever, involving the limbs. Indeed, the extremities may be cold, pale or have a dusky mottled hue during an attack. Over the areas of the blush are minute beads of perspiration. Lacrimation or merely watering of the eyes may occur without an associated emotional counterpart. These episodes occur without cause or may be brought on by embarrassment and excitement. The syndrome was called diencephalic because almost identical signs can be brought on by diffuse stimulation of the diencephalon in human beings."

Schroeder and Goldman [4] believe the syndrome is common, especially among patients exhibiting the "neurogenic" type of hypertension. They have grouped the symptoms and signs as disturbances of function of three components of the autonomic centers: "(1) Emotional instability can be seen by the excessive nervous tension and anxiety from which these patients suffer from time to time, as well as attacks of unreasonable weeping. These latter appear to bear no relation to the patient's inner emotional status at the time of the attack; she is unable to give a reason for her emotions which come on spontaneously at any time. (2) Vasomotor instability is shown by lability of the blood pressure, the characteristic blotchy blush on the skin and the recurrent episodes of cold, clammy, and pale or cyanotic extremities. (3) Autonomic instability is evidenced by excessive perspiration, attacks of polyuria, deep sighing respirations and the occasional presence of low grade fever. Sometimes the headaches they suffer occur only during such attacks."

Schroeder and Goldman [4] described a test using an intradermal injection of 0.25 mg. of histamine base into the volar surface of the forearm. They were able to reproduce attacks simulating the "hypertensive diencephalic syndrome" in 16 of 53 hypertensive patients and in but three normotensive subjects. Their 16 hypertensives all exhibited clinical signs of "neurogenic" hypertension.

We propose that the diencephalic syndrome be recognized as a specific type of "neurogenic hypertension." We have noted the relationship between the appearance of the syndrome and the occurrence of the menopause. It is interesting to note that the period of life during which the menopause appears is also the one in which essential hypertension is most likely to occur in women.

Page and Corcoran [5] were not impressed by the causal relationship of the menopause and essential hypertension. They studied a large group of women of different ages who had been subjected to hysterectomy and

oöphorectomy. Even after five to 10 years, hypertension was no more common in those surgically castrated patients than in normal women.

Our experience in the Hypertension and Nephritis Clinic of the Jewish Hospital of Brooklyn does not allow us to concur with this opinion. The largest percentage of the women admitted to the clinic date the onset of their symptoms or knowledge of their hypertension from the menopause. And many of these cases of hypertension, whose emotional, vasomotor and autonomic instability were accepted as part of menopausal derangement, we believe exhibit primarily the diencephalic syndrome. In some of this group, as was reported by Page and Corcoran,[5] the diagnosis of hyperthyroidism is suggested, since they may exhibit a slight diffuse enlargement of the thyroid gland and a basal metabolic rate that is often elevated to plus 30. In several of our cases of diencephalic syndrome, the excursions of blood pressure were so wide and the symptoms so dramatic that the diagnosis of pheochromocytoma was suspected. We have found the benzodioxan test helpful in differentiation.

The recognition of the diencephalic syndrome early in its course is important. By establishing an adequate treatment program, the attacks may be reduced to a minimum and the excursions of blood pressure confined to a low range, thus postponing or preventing sustained hypertension.

The symptoms and signs of diencephalic epilepsy are closely related to those of the diencephalic syndrome. The effective inhibitory action exerted by estrogens in controlling the diencephalic unrest in the case of diencephalic epilepsy led to a trial of a similar treatment program in the cases demonstrating the diencephalic syndrome. The results have been very satisfactory. An illustrative case follows:

Case Report

Case 2. A 46 year old white woman entered the Jewish Hospital of Brooklyn on January 19, 1945. She was admitted with a chief complaint of a lump in the abdomen. The past history included scarlet fever and pneumonia in childhood, and a kidney infection during her first of two pregnancies. She had had recurrent attacks of asthma and angioneurotic edema. For the past year and a half, the patient had noted a lower abdominal mass which was increasing in size.

On physical examination, her blood pressure was 135/80 mm. of mercury. There were moist, crepitant, post-tussive râles in the lower right chest. The abdomen revealed a smooth, firm, insensitive mass arising from the pelvis and extending up to the umbilicus.

Two urine specimens were not remarkable. A blood count revealed a hemoglobin of 77 per cent, with 3.76 million red blood cells. The white blood count and differential were normal. Roentgenogram of the chest showed no abnormal findings. A diagnosis of fibromyomata uteri and bronchiectasis was made. A hysterosalpingo-oöphorectomy was done and the patient was discharged.

The patient was readmitted to the Jewish Hospital of Brooklyn on September 27, 1946, with complaints of palpitation, headache, dizziness and a feeling of impending death. These symptoms all occurred in acute attacks.

These attacks had begun about two months after her operation. They occurred when the patient was up and about, rarely at rest. There was neither dyspnea nor

edema. Between the attacks, her blood pressure was normal: 120/80 to 130/84 mm. of mercury. The patient frequently became pale and collapsed during these seizures.

Physical examination was essentially negative, except for scattered râles throughout the right chest posteriorly.

The patient had a mild attack the second day in the hospital, which consisted of dizziness, headache and a rise in blood pressure to 190/100 mm. of mercury. On the following day she suffered a major attack. It began with a diffuse flush that spread over the face and upper half of the trunk. A pounding headache was her chief complaint. As the tempo of the headache increased, the skin became cold and colorless and she felt faint. The pulse increased in frequency and became irregular because of many premature contractions. The blood pressure rose to 260/110 mm. of mercury. The attack lasted 20 minutes and subsided without medication. A dull headache persisted for a few days.

A neurologic consultant saw the patient and found no evidence of objective pathology except the absence of both plantar reflexes. He thought that her difficulties were on an emotional basis. An intravenous pyelogram revealed moderate hydronephrosis on the right, with the superior calyx depressed and displaced forward. A retrograde pyelogram showed moderate dilatation of the right renal pelvis but no deformity of the calyces. Roentgenogram of the chest was not remarkable.

Electrocardiogram showed left axis deviation. All other laboratory data were within normal limits. The patient was afebrile throughout her hospital stay.

The diagnosis of pheochromocytoma was made but not confirmed.

On May 7, 1948, the patient had an attack while a guest at a social tea. This seizure began with a diffuse flush of the upper part of the body. As the headache became more intense, a drenching sweat covered the body. The skin became cold and pale. The pulse was rapid and many premature systoles were noted. The blood pressure rose rapidly to a peak of 265/115 mm. of mercury. This attack lasted 35 minutes.

Two days later, she was studied at the office (H. M.). The basal metabolic rate was plus 8. The blood pressure was 135/80 mm. of mercury. The heart was normal, the rate 72 per minute. An electrocardiogram showed left ventricular hypertrophy, regular sinus rhythm. A glucose tolerance test followed over a five-hour period was reported as normal.

On May 11, 1948, she suffered another severe attack and was admitted to the Jewish Hospital of Brooklyn the next day. She stated that a few months after her hysterectomy she had developed attacks of flushes and headaches. Several times since then the attacks had been severe enough for her to rest for a few hours because of extreme weakness.

During this admission she complained of "sinking spells." These "spells" were characterized by extreme weakness and "sinking," lasting 15 minutes and followed by explosive pounding in the chest and head, with accompanying blurred vision. The latter portion of the attack lasted about an hour and was followed by marked exhaustion. During these attacks, the patient's blood pressure rose from 115/80 to 210 mm. of mercury. On physical examination between attacks, her pulse was 84 per minute, respirations were 20 per minute, and her blood pressure was 130/80 mm. of mercury. Examination was negative except for a few râles at the base of the right lung.

Roentgenograms and laboratory work-up were not remarkable except that the electrocardiogram showed a more marked left axis deviation than that of September 27, 1946. She was completely afebrile.

The clinical impression was pheochromocytoma. However, the benzodioxan test (figure 1) was negative [6]; the pressor response suggested a diagnosis of diencephalic syndrome.

A treatment program of estrogenic hormone was outlined. She received 10,000 units three times weekly for four weeks, then twice weekly for the next three months.

Since April 10, 1946, she has had no attacks. She felt well enough to go to Europe five months later. There she continued estrogenic therapy (estrone .05 mg., orally, twice daily). However, after four weeks there was a recurrence of flushes and headaches. On her return, parenteral estrogenic therapy was again instituted. She has been free of major symptoms since. Her blood pressure has not exceeded 150/90 mm. of mercury.

In 52 cases demonstrating marked lability of blood pressure, the benzodioxan * test was used and proved helpful. In three of these 52 cases, the test was positive for pheochromocytoma.[6] The proof of these positive tests is awaiting the patients' consent to surgery.

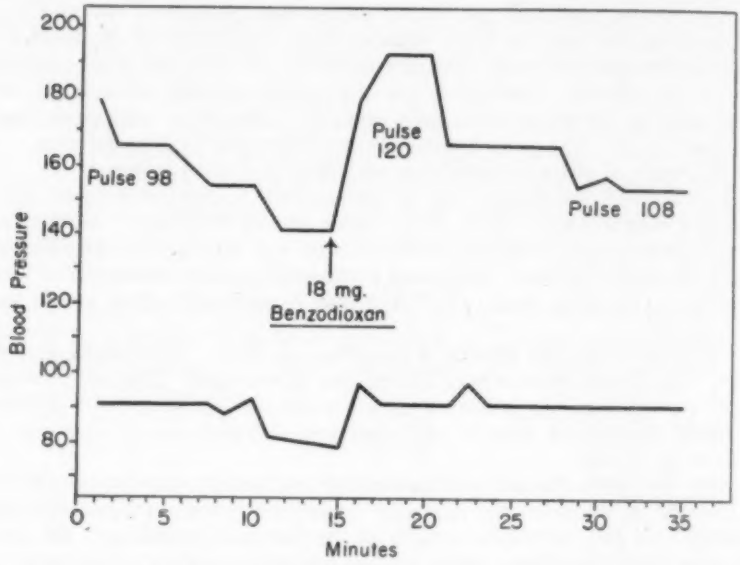

FIG. 1. *Case 2.* Pressor effect in response to injection of benzodioxan.

Of this group of 52 cases, 15 were males and 37 were females. In 12 cases of this group, the benzodioxan test resulted in a rise in systolic blood pressure of 40 mm. of mercury or more. We noted that there were 11 females and one male in this group and that, of these 12 patients, nine were between the ages of 44 and 55 years. We also noticed that this group contained most of the patients who exhibited the diencephalic syndrome. We are, therefore, suggesting that a rise in blood pressure of 40 mm. of mercury or more in the benzodioxan test be used as a presumptive test for the diencephalic syndrome.

* A generous supply of 2-(1-piperidylmethyl)-1,4-benzodioxan hydrochloride was given us by Merck & Co. Inc., Rahway, New Jersey.

Comments

Heretofore, we have not been satisfied with the results in these cases of treatment by sodium restriction, sedation and psychotherapy. The lability of the blood pressure characterizes the syndrome and, as the symptoms continue, there occurs a progressive rise in the resting blood pressure until ultimately high levels are sustained. As in the case of diencephalic epilepsy, estrogenic hormone proved effective in allaying the seizures exhibited by patients with the diencephalic syndrome. In several cases in which estrogenic hormone was faithfully continued, symptoms have abated to a large extent and the blood pressure has remained at or slightly above normotensive levels. One patient exhibited all the characteristics of the syndrome, with blood pressure peaks up to 275/145 mm. of mercury. She had a history of migraine and autumnal hay fever. Each injection of estrogenic hormone provoked local and systemic reactions. Attempts at desensitization proved unsuccessful. She was subjected to sympathectomy in 1942. The result in this case was unusually good. (Similar good results were reported in three cases by Schroeder and Goldman.[4])

Summary

We have presented a case of diencephalic epilepsy due to mumps encephalitis. The patient exhibited a wide range of emotional symptoms, including rage and libido. Vasomotor instability and autonomic functional disturbances were manifold. These included skin changes, perspiration, wide fluctuations in blood pressure, irregularity of heart rhythm due to premature contractions, changes from hypothermia to low-grade fever, diabetes insipidus, occasional glycosuria, colonic irritability, and dysmenorrhea and menorrhagia. Somatic tremors recurred frequently. Sedation proved of no value. Large doses of estrogenic hormone resulted in establishing a remission.

The diencephalic syndrome is more common. It embodies the characteristic emotional, vasomotor and autonomic disorders described above. Here again, adequate dosage of estrogens controlled the symptoms. Moreover, the treatment program with estrogens has been effective in delaying the appearance of sustained hypertension in many of these patients.

The benzodioxan test proved useful in differentiating cases of diencephalic syndrome from those of pheochromocytoma.

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THE CLINICAL VALUE OF UNIPOLAR EXTREMITY (aV) LEADS*

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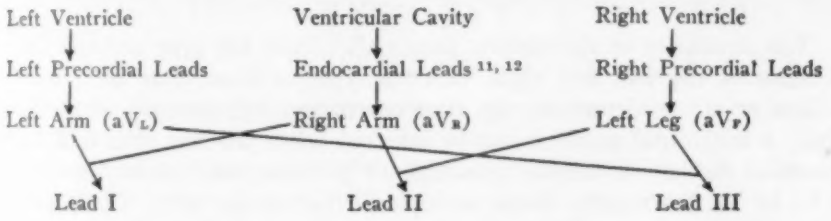
THE practical clinical value of multiple precordial unipolar leads has been clearly established.[1, 2, 3, 4, 5, 6] Not so well appreciated and, in fact, in some quarters doubted, has been the clinical aid obtained from unipolar extremity leads.[7, 8, 9, 10] The present study was made to define and illustrate the possible added advantages of unipolar extremity leads.

It has been noted by Wilson and his associates,[1] Goldberger,[3] and Myers and his associates [7] that the unipolar extremity leads are, in effect, highways that link the precordial leads with the standard limb leads.

The precordial leads register most directly the potential changes occurring in the heart, and one must not forget that it is the myocardial changes that one wishes to record by taking electrocardiograms. Extremity and standard limb leads indirectly indicate myocardial changes because the potential changes from the heart are transmitted to all parts of the body in consonance with the concept that the body serves as a volume conductor. The unipolar extremity leads reflect changes in either the left or the right ventricle, depending upon the position of the heart. The standard limb leads are derived from the unipolar limb leads, and therefore one can better understand standard leads if one understands the immediate parent source, the unipolar extremity leads. The relationship in a horizontal heart can be illustrated as follows:



It is seen that the standard leads are the most indirect and empiric of all the possible electrocardiographic leads. They are bipolar, and differences between, for example, the right arm and the left arm would be reflected in Lead I. But if the potential at both the left arm and right arm altered in the same direction and in the same degree, the changes would not necessarily

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be reflected in Lead I. In this way, significant changes might appear in the left or right arm without significant abnormalities appearing in Lead I.

Wilson and his associates [1] have noted that the precordial leads are, in effect, semidirect leads from the epicardium and reflect in greatest degree changes directly under the electrode. This feature is valuable when one is interested in defining localized myocardial lesions. The effects of distant myocardial areas are proportionately less as those areas are farther away from the precordial lead. Yet, depending upon the position of the heart and the electrical axis, the unipolar extremity leads may register changes from any portion of the heart facing the extremity. In this way, the left arm lead may reflect lateral myocardial abnormalities not obtained from an electrode in position V_5 or V_6.

TABLE I

The Ventricular Deflections in the Unipolar Extremity Leads (Measurements in Millimeters)

Lead		Normal (150 Cases)				Normal—Left Axis Deviation (21 Cases)				Normal—Right Axis Deviation (19 Cases)			
		Mean	±St. Dev.	Min.	Max.	Mean	±St. Dev.	Min.	Max.	Mean	±St. Dev.	Min.	Max.
aV_L	Q	0.2	0.5	(0	3.5)	0.5	0.4	(0	1.0)	0.1	0.2	(0	3.5)
	R	2.1	2.1	0	10.0	4.6	2.5	0.5	10.0	0.9	0.8	0	3.0
	S	0.4	3.9	0	18.0	0.3	0.7	0	3.0	0.5	3.6	0	18.0
	T	0.53	1.26	−4.0	+6.0	1.0	0.81	−1.0	+2.5	0.45	1.0	2.0	+2.0
aV_R	Q	2.0	3.7	0	8.0	1.0	2.6	0	6.0	1.8	2.7	0	8.0
	R	0.8	0.9	0	5.0	0.4	0.6	0	1.5	0.8	0.8	0	3.5
	S	4.3	4.0	0	13.0	4.3	0.9	0	8.0	4.3	4.6	0	13.0
	T	−2.31	0.92	−5.0	+1.5	2.2	0.67	−3.0	+1.0	−2.08	0.84	−4.0	−1.0
aV_F	Q	0.5	1.4	0	3.0	0.4	1.0	0	5.0	0.7	0.2	0	2.0
	R	1.3	8.3	0	20.0	2.7	2.2	0	8.0	10.5	4.2	0.7	20.0
	S	0.2	1.3	0	8.0	1.6	1.4	0	4.0	0.4	2.1	0	2.0
	T	1.86	1.1	−0.5	+5.0	1.4	0.92	−0.5	+3.0	1.84	0.96	+0.5	+4.0

The similarity of the electric potentials of the left arm and the left leg to those of the left and right ventricle (precordium) has been used by Wilson et al.[1] to determine the electrocardiographic position of the heart. Thus, a horizontal position can be inferred when the left arm lead (aV_L) resembles the left ventricular potentials or patterns, such as are usually seen in V_5 or V_6, but may be found in leads further to the left. These patterns of left ventricular potentials are represented by qRs, qR or Rs in type. In horizontal hearts, if abnormalities are found in aV_L and not in V_5 or V_6, the routine left precordial leads, then it is clear that the source of the abnormalities most probably was an area of the left ventricle other than that subjacent to V_5 and V_6. In this way, lead aV_L may direct attention to the need for further exploration of the chest in an attempt to find the site of the left ventricular abnormality. Similarly, abnormalities in aV_F in a vertical heart, with relatively normal V_5 and V_6, would suggest to the electrocardiographer that exploration of the posterior left chest may prove profitable. Examples of this use of the unipolar extremity leads will be illustrated later.

It becomes important to define the normal range of the unipolar extremity leads, and table 1 is taken from the paper of Sokolow and Friedlander,[18] who utilized 150 normal subjects. Augmented leads using the technic of Goldberger were employed.

With particular reference to T waves, it may be noted that in no normal subject was the T wave upright in aV_R. The T wave was frequently inverted in aV_L in vertical hearts, but the inversion rarely exceeded 1 to 1.5 mm. When the R wave was greater than 6 mm. in aV_L, the T wave was not inverted in normal subjects. The T wave in Lead aV_F was found rarely in horizontal hearts to be diphasic, but not clearly inverted more than 0.5 mm. When the R wave in aV_F was taller than 6 mm., no normal subject was found to have inverted T waves in aV_F.

The details of the various types of unusual rotations involving the various axes of the heart have been reported by Goldberger [8] and by Myers and Klein,[7] and will not be discussed here.

Methods and Subjects

The material available for study was obtained from the daily records of the department of electrocardiography of the University of California Hospital. Between 1945 and 1948, 5,000 patients have had routine and special studies with standard, unipolar precordial and unipolar extremity leads. Many patients have had repeated or serial electrocardiograms. When indicated or thought advisable, exploratory leads over the right, left, lateral or posterior chest were made. These will be adequately illustrated. Many of the patients were seen personally; all of those to be described, if not seen personally, have had their clinical charts and roentgen films of the chest reviewed. In practically all cases it was possible to discuss with the patient's physician details of the case that might not have been adequately recorded in the chart.

Results

Study of the unipolar extremity leads proved helpful in a variety of conditions:

1. Abnormalities in these leads have been found with normal or doubtful findings in the remainder of the electrocardiographic study.

2. Abnormalities in the extremity leads might be more typical of a given electrocardiographic pattern than would other leads, although the precordial leads might also be abnormal; yet the information obtained was clearly of value.

In many cases, of course, the precordial leads were quite typical of the pattern present, and the extremity leads were less typical or even within normal limits. The last was most apt to be found in anteroseptal lesions.

The major situations in which unipolar extremity leads were found of significant value, independent of or in addition to the precordial and standard leads, were as follows:

I. The Significance of a Q or QS Complex in Lead III. The interpretation of a Q wave in Lead III has always been a vexing problem. A Q wave will appear in Lead III whenever the initial ventricular potential of the left leg is negative as compared to that of the left arm. When records are taken in the usual fashion, allowance must be made for the fact that aV_L

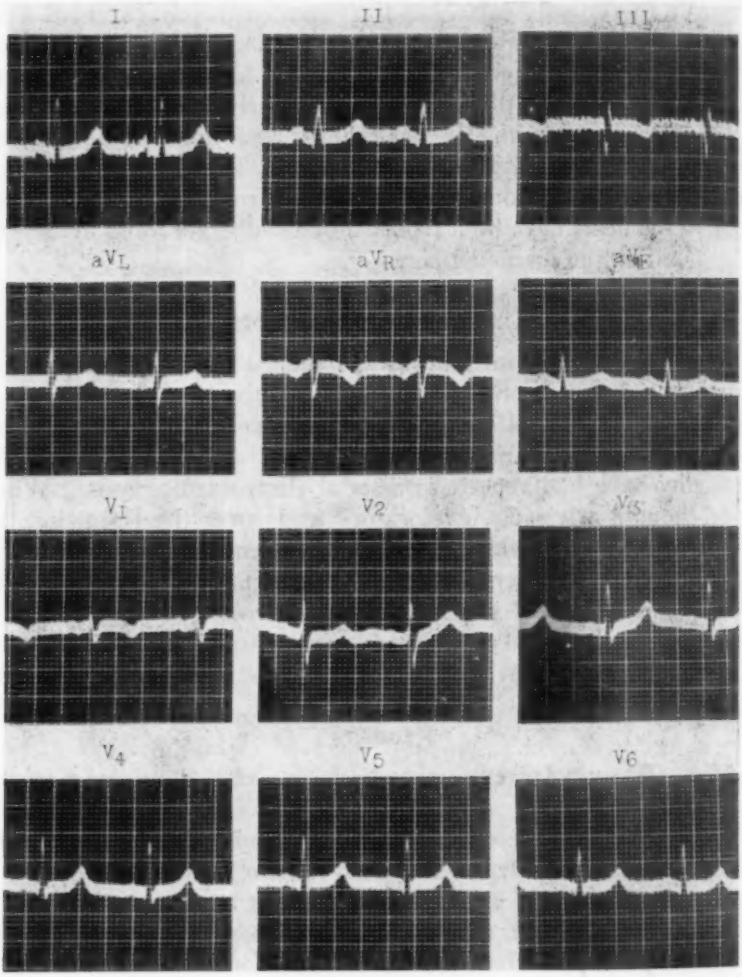


FIG. 1. A patient with obesity and a normal heart in the intermediate position.

and aV_F are not taken simultaneously. There are several possible combinations of circumstances in which a Q_3 may be present without a Q wave being present in the left leg lead, because such may occur whenever the initial deflection in aV_F is relatively negative to aV_L, even though both are positive. In posterior myocardial infarction, electrical changes from the

posterior diaphragmatic surface of the left ventricle are transmitted to the left leg. A Q_3 significant of posterior myocardial infarction is therefore one which reflects a significant Q wave in the left leg lead. Study of the normal subjects [13] has indicated that the normal Q in aV_F is less than 30 per cent of the R in aV_F when the total QRS voltage exceeds 5 or 6 mm.; a myocardial infarction should be suspected when this figure is exceeded, especially if the total QRS voltage in aV_F is greater than 7 mm. Myers and his associates [7, 10, 14] have also stressed the fact that the duration of the normal Q wave from its onset to nadir does not exceed 0.03 second. Study of aV_L and aV_F can explain, therefore, the Q wave that appears in Lead III, and permit an interpretation as to whether it merely reflects predominant positivity of the left arm (as in horizontal hearts due to obesity, e.g., R. A., female, figure 1), or whether it indicates significant negativity of the left leg (as in posterior myocardial infarction). The six precordial leads are often within normal limits in posterior infarction, and electrocardiographic diagnosis must rest on characteristic findings in Lead aV_F. On occasion, Lead aV_F is conclusively abnormal while Lead III is not; very rarely the reverse is true.

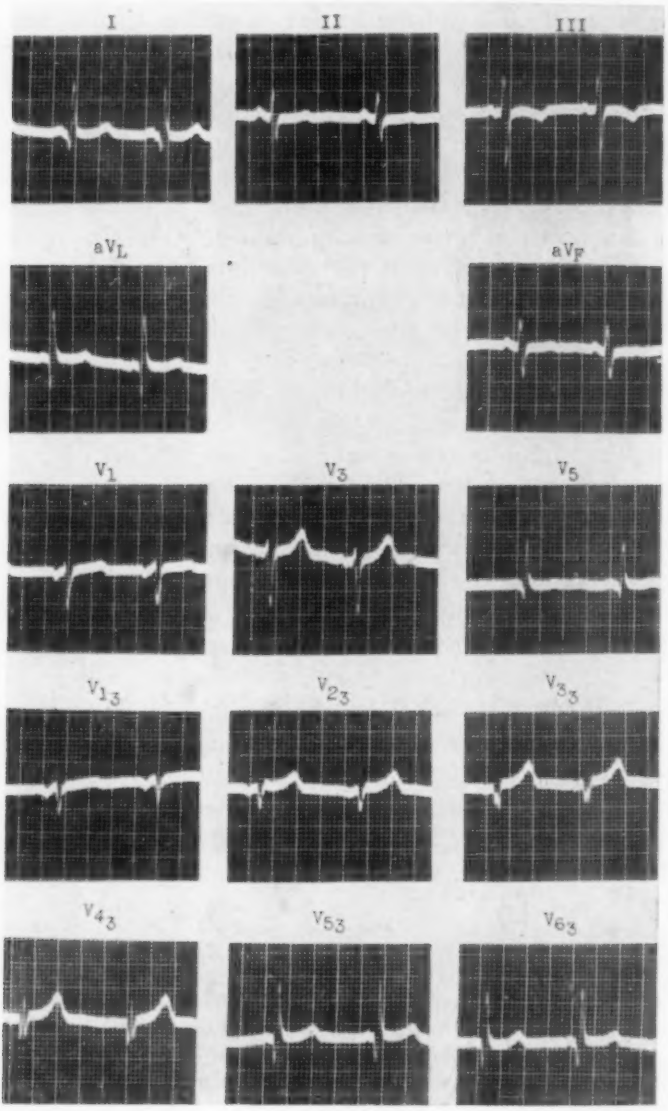
II. Anterior Myocardial Infarction. Rosenbaum, Wilson, and Johnston [15] have demonstrated that high precordial leads may reveal the typical findings of myocardial infarction when the routine precordial leads are equivocal. Myers and his associates [14, 16, 17, 18, 19] have also commented on this fact. The left arm lead, in their cases, was usually the clue that directed the electrocardiographer to study leads from different points on the chest. We have similarly found that the presence of an abnormal Q or T wave in Lead aV_L was occasionally the only or major abnormality in the routine record. Exploratory leads in the second, third and, rarely, sixth interspace as far laterally as the 10 position were at times rewarding. There were occasional patients in whom typical electrocardiographic findings of myocardial infarction, with characteristic Q, ST and T changes, were localized in only one or two chest positions; leads from other positions on the chest showed abnormalities, but they were not diagnostic of infarction. The following cases are illustrative.

Case Reports

Case A. S. A 62 year old female (figure 2) gave a history of myocardial infarction two years before entry, and dyspnea on effort ever since. The electrocardiogram revealed a deep Q in aV_L and a low to flat T in V_5 as the noteworthy findings in the routine 8-lead record. Leads from the third interspace revealed a wide, notched Q or QS in V_2 through V_4, and deep Q waves in V_{5_3} and V_{6_3}. The Q wave in V_{5_3} is distinctly deeper than that in the routine V_5.

Case R. P. A 55 year old male (figure 2) had a myocardial infarction in 1945. In the routine record, a low T_1 and a Q wave in aV_L, borderline in character, were the only noteworthy findings. Third interspace leads were taken because of the history and the QaV_L. These showed a notched Q in V_3 and a Q in V_4 deeper than that in V_6.

Case A. M. R. A 39 year old male (figure 3) had cirrhosis of the liver and complained of a bout of epigastric pain, the significance of which was at first doubtful. Myocardial infarction was suspected because of associated dyspnea and sweating. Frequent serial electrocardiographic records were obtained. The earliest abnormalities were seen in Lead aV_L and later in Leads V_7 and V_8 and Lead I. The progressive changes in T wave contours supported the diagnosis of myocardial infarction.



A

FIG. 2. A and B. Two patients with clinical myocardial infarction in whom Q waves in Lead aV_L led to further exploratory leads high over the precordium, revealing significant abnormalities in the third interspace leads.

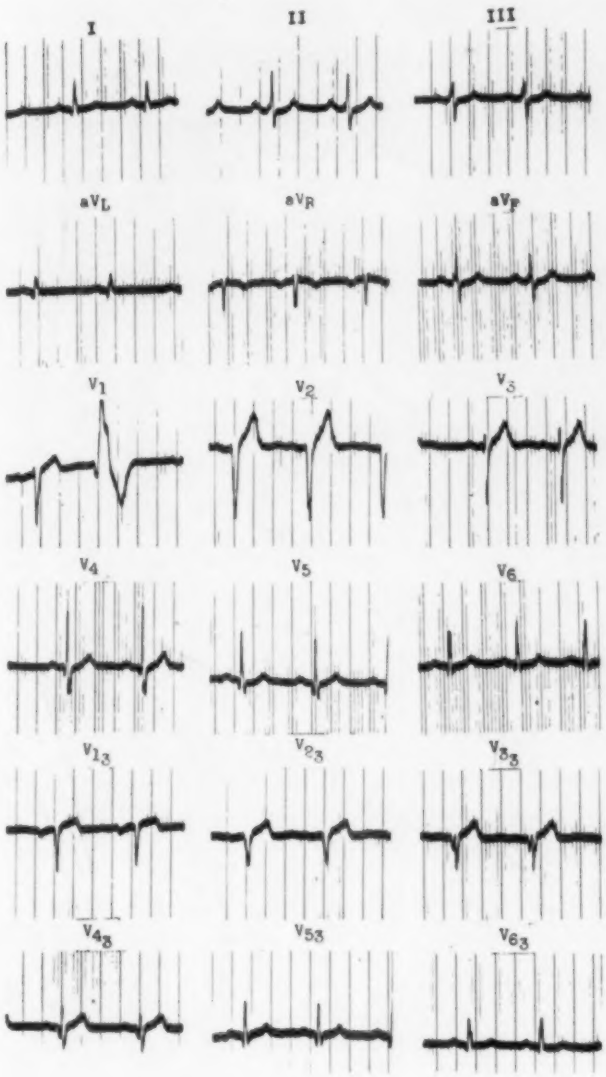


FIG. 2B

Cases W. J. D. and M. W. A 74 year old male and a 54 year old female (figure 4) are patients with coronary heart disease and angina pectoris in whom Lead aVL was valuable in diagnosis. In the male patient, W. J. D., the T wave in aVL was clearly and abnormally inverted, despite normal T waves as far to the left as the 7 position in both the third and fifth interspaces. The female, M. W., also had abnormally inverted T waves in aVL, with upright T waves as far to the left as the 8 position in the fifth interspace. However, the T waves were inverted from the 3 to the 6 positions in the third interspace. This patient may well have had a high anterior myocardial infarction, although the clinical history was not typical.

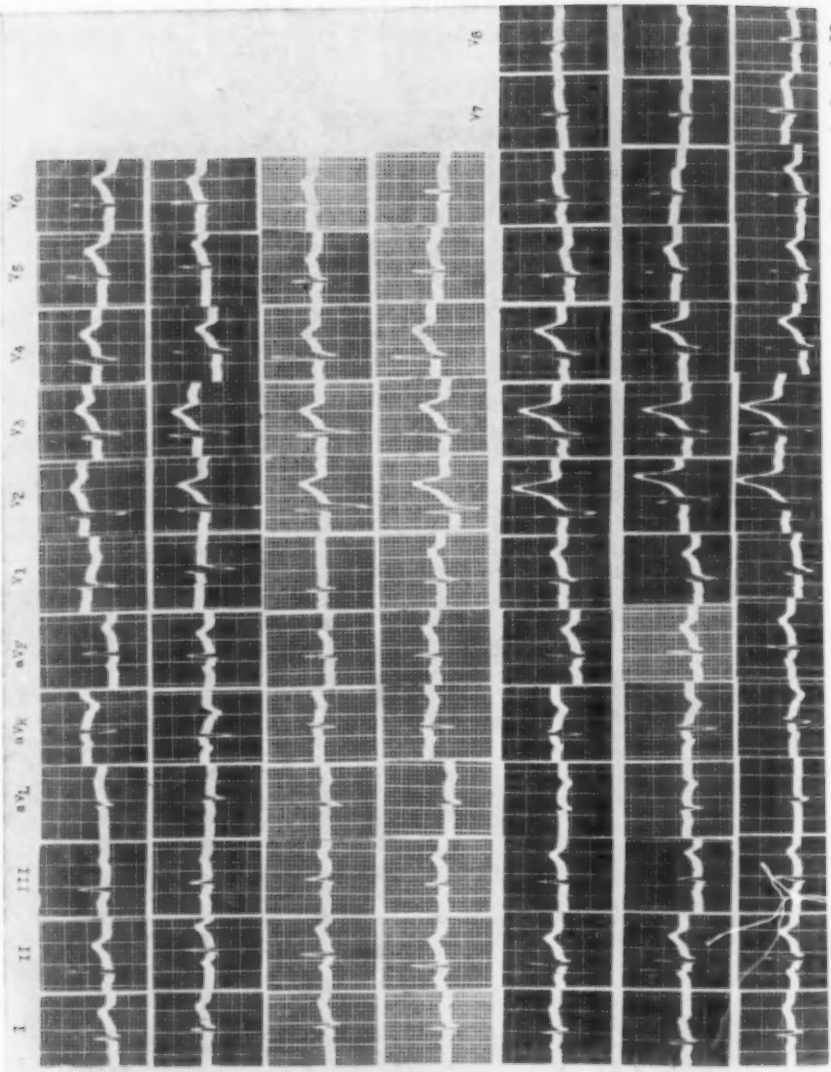


FIG. 3. A patient with lateral myocardial infarction in whom progressive inversion of the T waves in Lead aV$_L$ represented the earliest abnormalities.

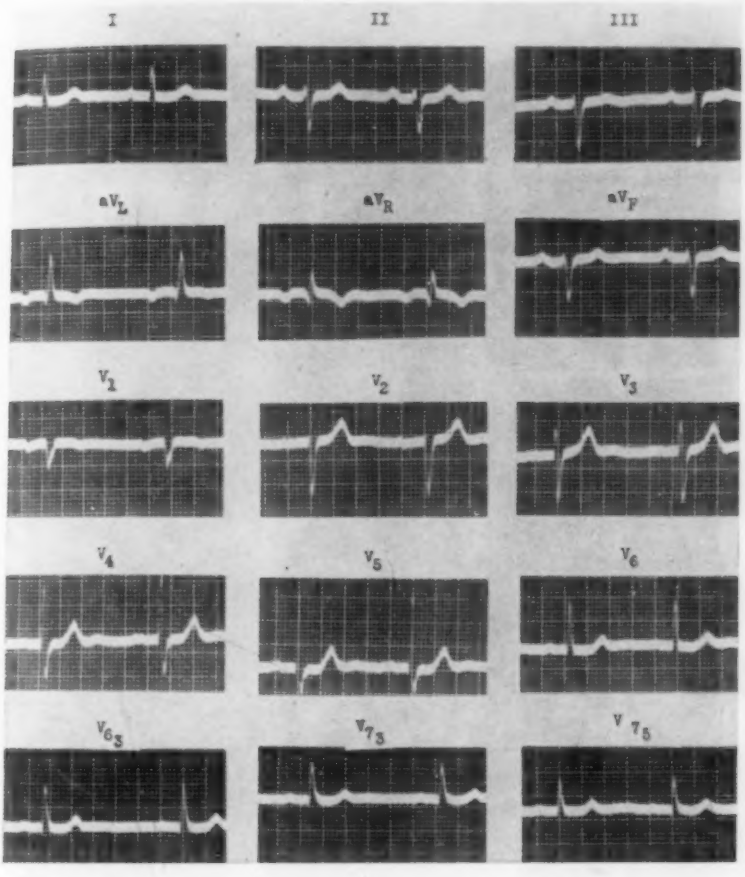


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FIG. 4. A and B. Two patients with coronary heart disease and angina pectoris in whom Lead aV_L revealed the significant electrocardiographic abnormalities. In the lower example, third interspace leads revealed the source of the inverted T waves noted in aV_L.

III. Left Ventricular Hypertrophy. The characteristic electrocardiographic pattern of left ventricular hypertrophy has been detailed recently in this laboratory.[20] The typical changes in voltage and in ST–T configuration usually appear first and most strikingly in the left precordial Leads V_5 and V_6. Depending on the position of the heart, the abnormalities may then appear in aV_L (horizontal hearts) or aV_F (vertical hearts). Occasionally the only, or the most typical, abnormalities may appear solely or initially in the unipolar extremity leads and so be of major diagnostic aid in demonstrating the presence of left ventricular hypertrophy. The following cases are representative.

Case C. S. A 45 year old female (figure 5) had had hypertension since 1935. Cardiac enlargement of plus 10 per cent * had been noted in 1946. An electrocardio-

* Ungerleider table.

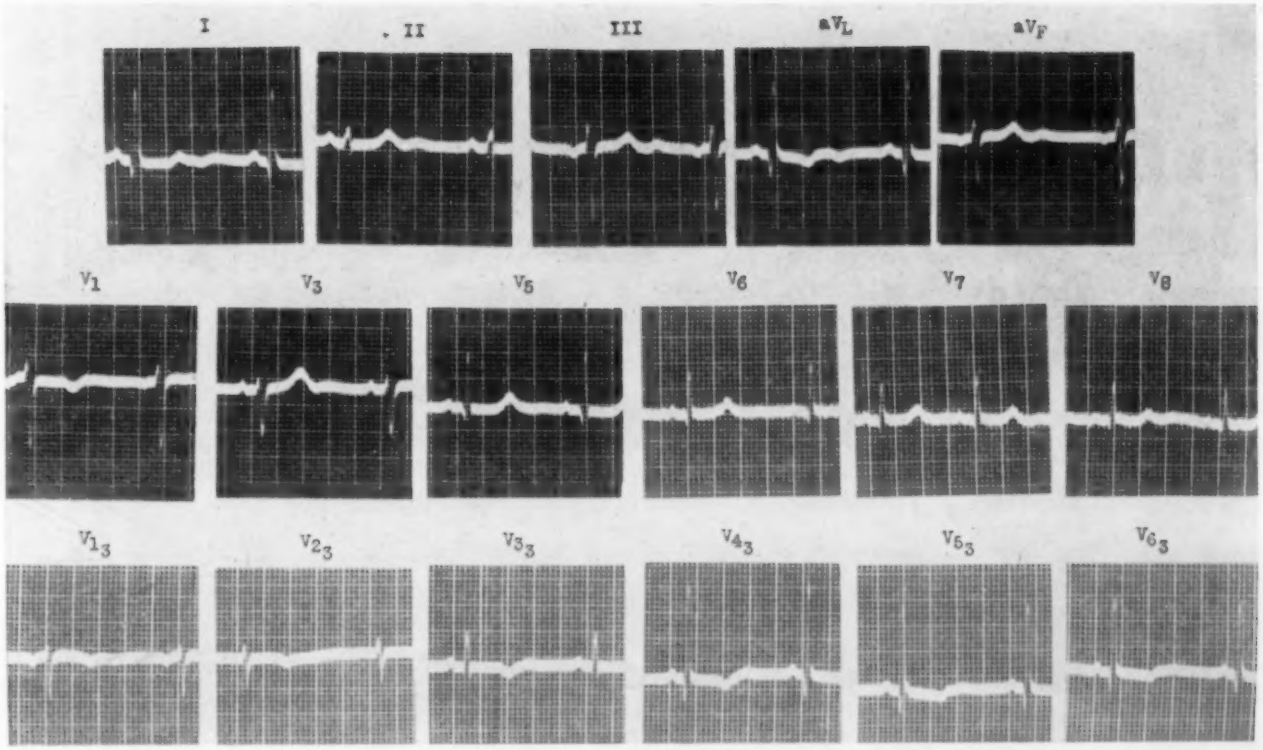

FIG. 4B

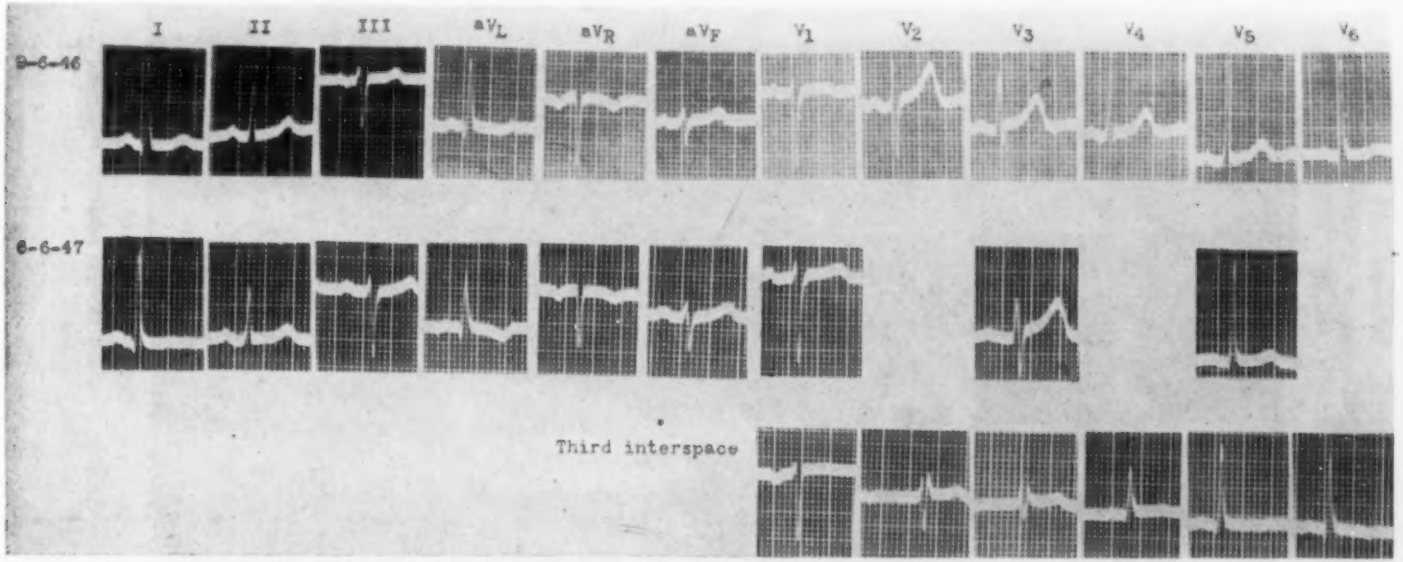

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FIG. 5. A and B. Two patients with left ventricular hypertrophy due to hypertension in whom the earliest abnormality in routine leads was found in Lead aV_L. In the upper example, high voltage QRS and relatively low T waves are seen in V_5 and V_6. The progressive changes between September 6, 1946 and June 6, 1947 are most clearly seen in Lead aV_L.

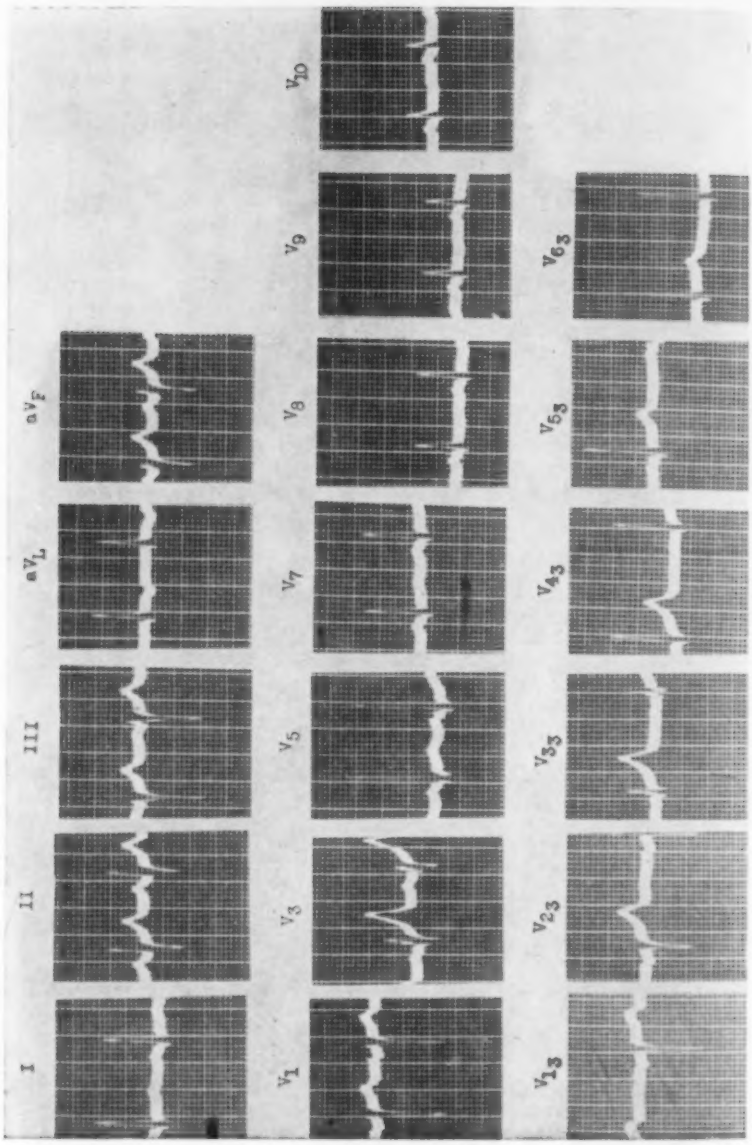


FIG. 5B

gram taken in September, 1946, revealed a slightly depressed ST segment, diphasic T wave, and a tall R wave in aV_L as the major abnormality. T_1 and TV_6 are relatively low but clearly upright. The $T_1 : T_3$ ratio is abnormal, but this is due to the abnormality of TaV_L. The voltage of R in Lead I is at the upper limits of normal. In the record of June 6, 1947, nine months later, the T wave in aV_L is more deeply inverted, while that in V_6 is still low, upright, and the T wave in Lead I is flat. The

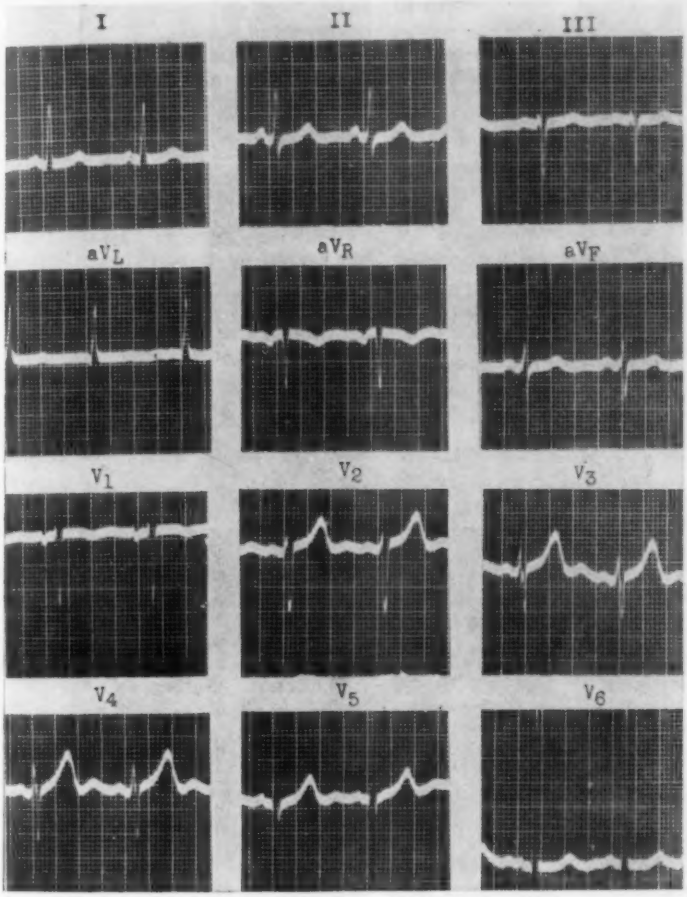


FIG. 6. A patient with left ventricular hypertrophy due to hypertension demonstrating the earliest abnormality of the T wave in Lead aV_L. V_6 reveals high voltage of the QRS complex and a low T wave.

voltage of QRS in the standard leads has increased so that $R_1 + S_3 = 27$ mm. Third interspace leads on June 6, 1947, showed a flat T wave in V_6 and a diphasic T wave in V_6. These records show that the earliest sign of left ventricular hypertrophy was found in Lead aV_L in this horizontal heart. In addition, leads in the third interspace were more abnormal than leads from comparable positions in the fifth interspace.

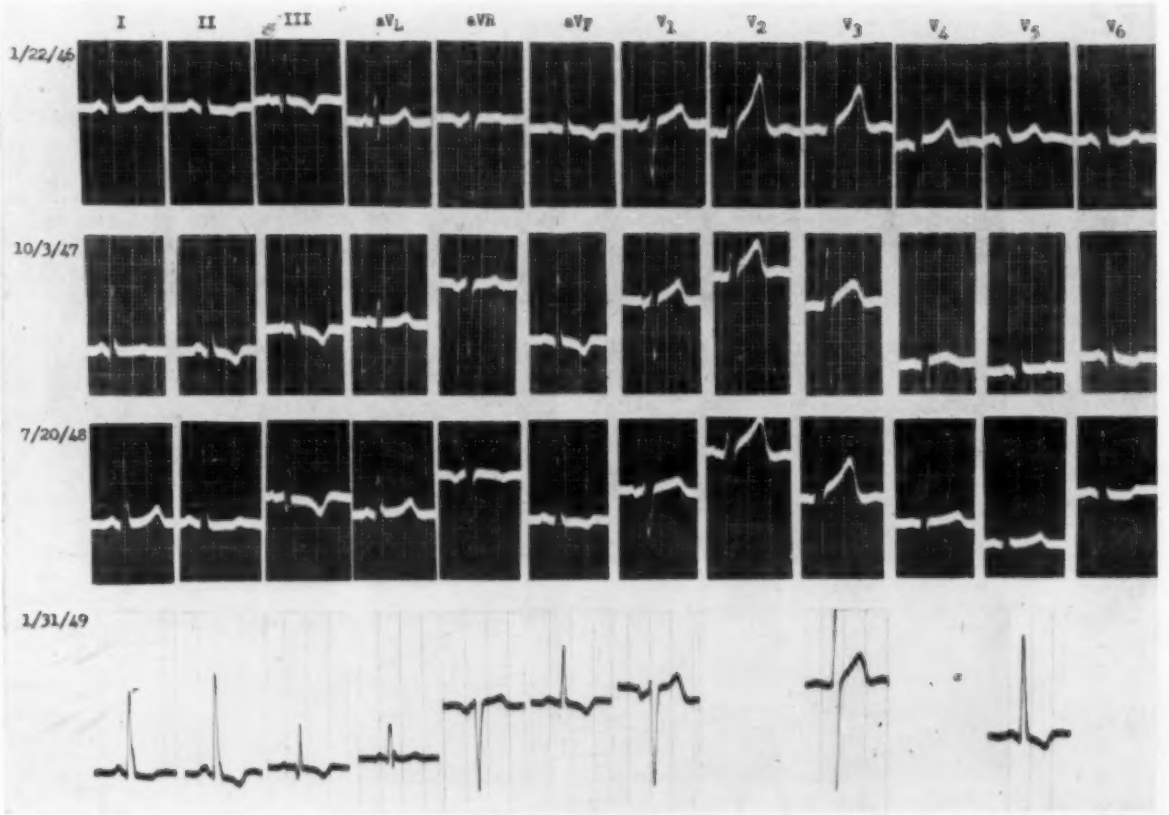


FIG. 7. A patient with left ventricular hypertrophy due to coarctation of the aorta. The earliest abnormalities in this semivertically placed heart were found in Lead aV_F on January 22, 1946.

Case S. B. A 50 year old male (figure 5) is a patient with hypertension. Cardiac enlargement of plus 13 per cent was demonstrated by roentgenogram. The electrocardiogram revealed an inverted T wave in aV_L, with upright T waves in the seven precordial leads in both the third and fifth interspaces. Flat to slightly diphasic T waves were noted in V_{8-9}, and small, slightly inverted T waves were found in V_{10}.

Case A. D. A 36 year old female (figure 6) had hypertension with cardiac hypertrophy + 20 per cent revealed by roentgenogram of the chest. In this patient, the T wave was low, diphasic in aV_L with an R wave of 10 mm. T in V_6 was upright, 1.5 mm., with a tall R wave. The major abnormality of the T wave was therefore seen in Lead aV_L.

In vertical hearts, similar examples were found regarding the value of aV_F in the diagnosis of left ventricular hypertrophy.*

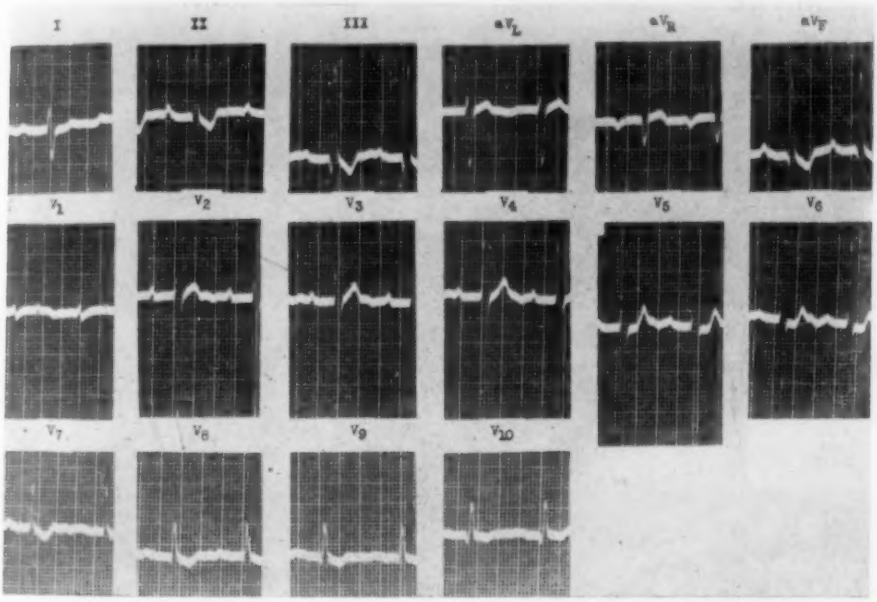
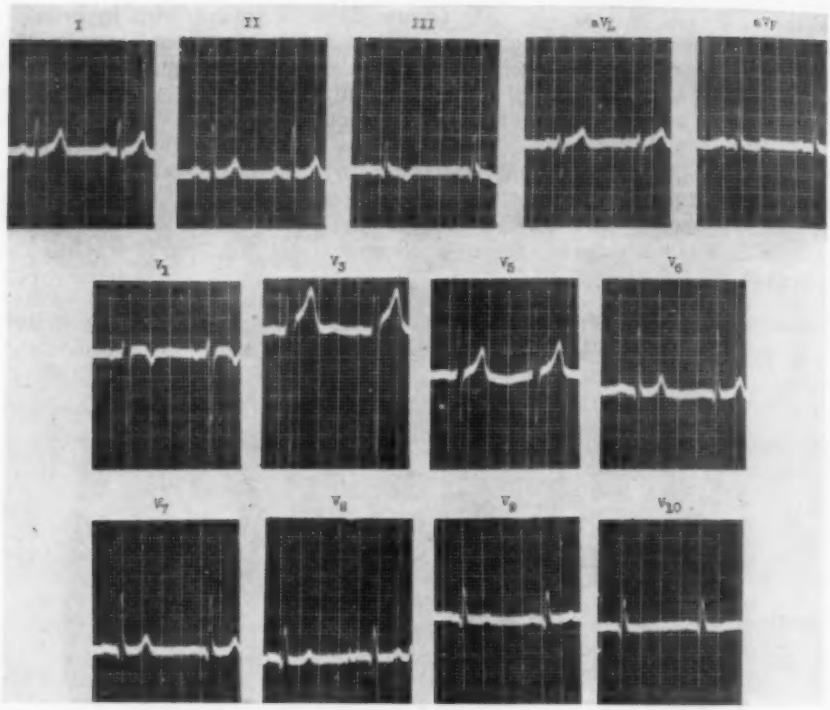


FIG. 8. A patient with left ventricular hypertrophy due to congenital heart disease proved by angiocardiography. The right axis deviation and deep S wave in V_6 simulated right ventricular hypertrophy. But the changes in Lead aV_F led to left exploratory leads V_7 through V_{10} permitting the diagnosis of left ventricular hypertrophy.

Case D. H. This case of a 25 year old male (figure 7) represents serial records of a patient with coarctation of the aorta and a transverse diameter of the heart + 20 per cent above normal. In the tracing of January 22, 1946, the T wave in V_6 is upright, but T in aV_F is clearly inverted with a tall R wave. T in Lead II is diphasic and in Lead III is inverted. The *major* abnormality is aV_F. The electrocardiogram of October 3, 1947, shows that the abnormalities have progressed: T in V_6 is now diphasic and T_3 clearly inverted. T in aV_F is more deeply inverted. High voltage QRS is seen in the precordial leads. Spontaneous improvement in the electrocardio-

*Subsequent work in our laboratory has demonstrated inverted T waves at ventricular levels in esophageal leads in these cases with inverted T waves in aV_F.



A

FIG. 9. A, B and C. Three cases of left ventricular hypertrophy in vertical or semivertical hearts demonstrating the value of Lead aV_F in diagnosis.

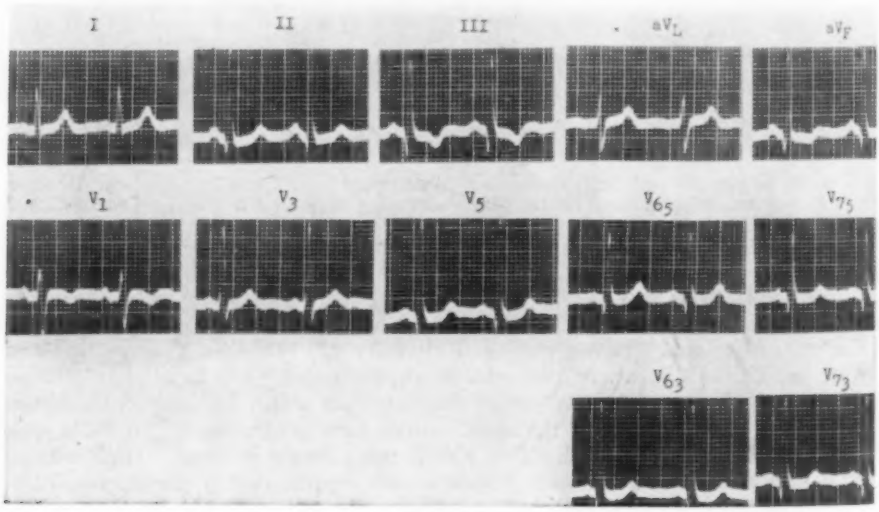


FIG. 9B

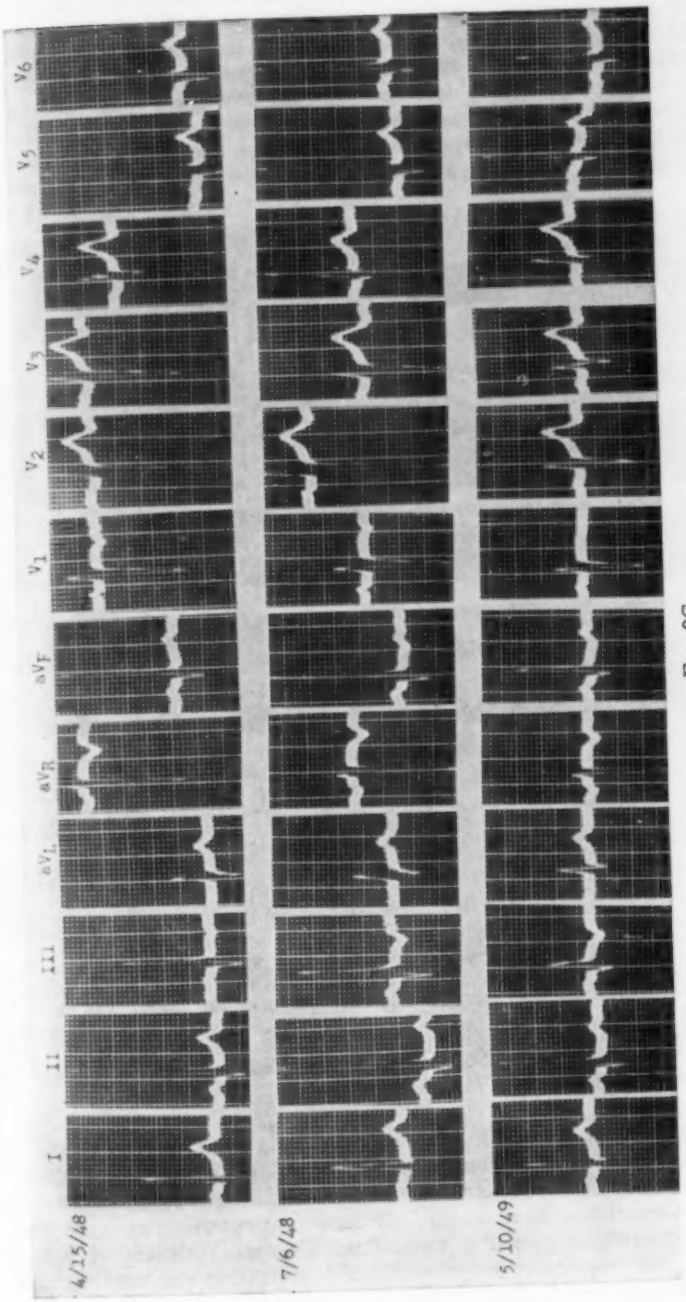


FIG. 9C

gram is apparent in the record of July 20, 1948, but the changes have again progressed by January 31, 1949.

Case M. S. A 30 year old female (figure 8) had congenital heart disease with a large pulmonary artery, and cardiac enlargement of + 60 per cent. The standard limb leads revealed right axis deviation with an inverted T wave and tall R waves in Leads II and III. In addition, there was a deep S wave in V_6. These findings suggested right ventricular hypertrophy. However, the tall R wave and absent S wave with inverted T wave in aV_F in the presence of a vertical heart indicated that

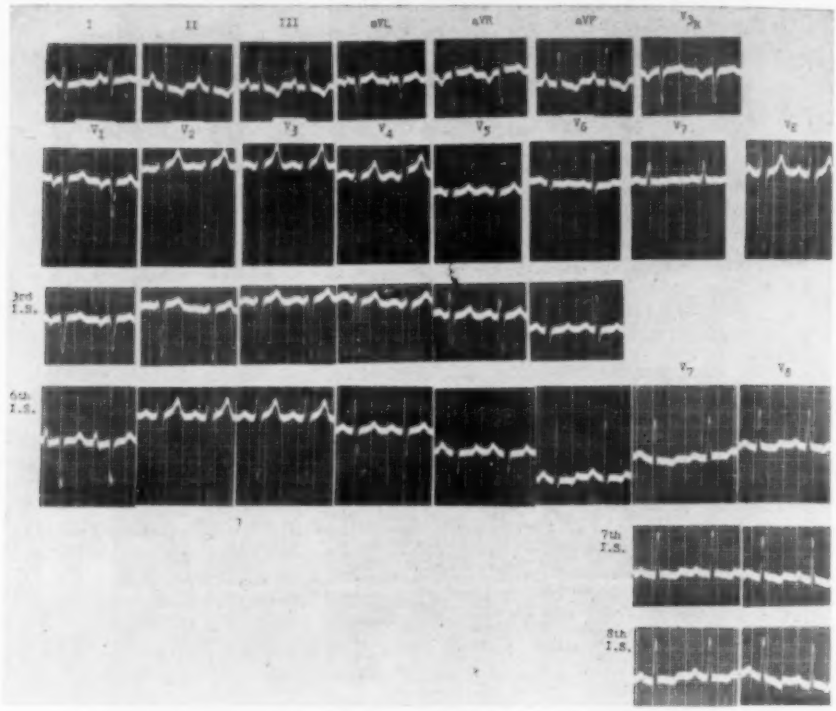


FIG. 10. Left ventricular hypertrophy secondary to hypertension in a patient with emphysema and a low diaphragm. The diagnostic value of Lead aV_F in indicating the need for further exploration of the chest to find the source of the inverted T wave in aV_F is shown by the normal appearing V_6 and V_7 in the fifth interspace, and the abnormal ST-T complex in V_6 and V_8 in the sixth interspace and V_7 and V_8 in the seventh and eighth interspaces. Therefore, the myocardial abnormality was noted in low precordial leads and transmitted to the left leg lead.

V_6 did not reflect the left ventricular potential, and leads farther to the left of V_6 were taken. These revealed complexes in V_7 through V_{10} similar to those seen in aV_F, and indicated that the patient had left ventricular hypertrophy in a vertical heart, and not right ventricular hypertrophy. Diodrast angiocardiograms confirmed the left ventricular hypertrophy. In this case, Lead aV_F was valuable in permitting the diagnosis of left ventricular hypertrophy and indicating the need for further exploratory leads.

Case A. B. C. This 15 year old female (figure 9) had patent ductus arteriosus. The chest film revealed cardiac enlargement of + 14 per cent. Note the changes

between records of April 15, 1948, July 6, 1948, and May 10, 1949. The ductus was ligated on July 20, 1948. The inverted T wave in Lead aV_F was the only abnormality consistent with left ventricular enlargement. The appearance of the electrocardiographic abnormality following surgery is of interest and has been seen in several of our cases.

Case R. H. This case is also a 15 year old female (figure 9) who had patent ductus arteriosus. A chest film showed left ventricular hypertrophy with cardiac enlargement of + 11 per cent. An abnormal T wave in aV_F was the only significant finding in the electrocardiogram.

Case F. D. S. This 25 year old male (figure 9) had rheumatic heart disease with aortic stenosis and insufficiency. The heart was enlarged + 15 per cent. An abnormal diphasic T wave with an R wave of 9 to 10 mm. was noted in aV_F. The T waves were normal in V_5 through V_8, and the T wave was low to diphasic in V_9 and V_{10}.

Case L. G. R. This case of a 62 year old male (figure 10) illustrates the importance of Lead aV_F in demonstrating abnormalities that arise from potential changes inferior and lateral to the usual left precordial leads. This patient had silicosis and hypertensive cardiovascular disease with cardiac enlargement of + 25 per cent. The inverted T wave in Lead II and Lead III with right axis deviation suggested the possibility of right ventricular hypertrophy, but there were no confirmatory signs in V_1, V_{3R} or aV_R.[1, 21, 22, 23, 24] Furthermore, the appearance of Lead aV_F suggested that V_6 and V_7 did not reflect the entire left ventricular pattern. Because of the emphysema and low diaphragm, leads were taken in the sixth, seventh and eighth interspaces, and it will be seen that aV_F resembles V_7 and V_8 in these interspaces. Since exploratory precordial leads are not always convenient in routine practice, the value of Lead aV_F in this case was considerable in indicating the presence of left ventricular hypertrophy in a vertical, more inferiorly-placed heart.

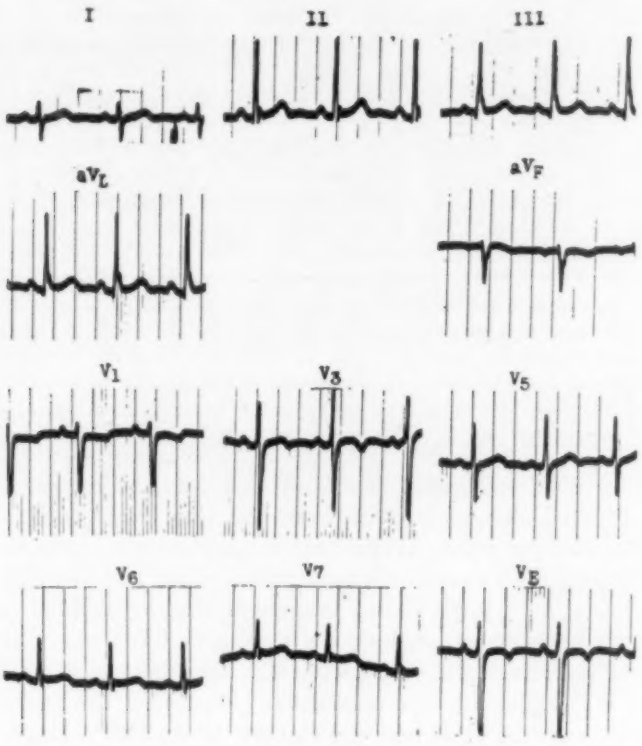
IV. Displaced Transitional Zone. When the heart is rotated clockwise on its longitudinal axis, as viewed from the apex, the transitional zone is often displaced to the left. When this displacement occurs, records taken from the V_4 through V_6 positions may reflect right, and not left, ventricular potentials, revealing a small R and prominent S wave such as one normally obtains from the right precordium. The routine left precordial leads may, therefore, fail to reveal abnormalities which may be found when leads further to the left (reflecting left ventricular potentials) are taken. In addition, the left precordial leads may then appear to support a diagnosis of right ventricular hypertrophy in which prominent S waves and small R waves are typical. In these situations, study of the unipolar extremity leads (aV_L in horizontal hearts and aV_F in vertical hearts) will permit one to determine whether the true left ventricular potentials are correctly reflected by the V_4 through V_6 leads. (See Case M. S. under left ventricular hypertrophy.) [4]

Case T. T. This was a 34 year old male patient (figure 11) with moniliasis and pulmonary fibrosis but no cardiac abnormality. The electrocardiogram showed a deep S wave in V_5 suggesting right ventricular hypertrophy. However, aV_L has a monophasic tall R wave. This, in the presence of a horizontal heart, indicated that V_5 was taken to the right of the transitional zone.

Case J. A. J. This case of a 66 year old male (figure 11) reveals that the transitional zone is located between V_6 and V_7. This patient had asthma and slight emphysema. The deep S wave in V_5 suggested right ventricular hypertrophy, but the tall

R in aV_F in the presence of a vertical heart indicated that V_6 did not reflect the true left ventricular potential. Leads further to the left confirmed this fact, and in V_7 the S wave has largely disappeared.

Displacement of the transitional zone to the right beyond the V_2 position is infrequently seen, but when it does occur the electrocardiogram suggests the presence of right ventricular hypertrophy, because V_1 and V_2 have prominent R and small S waves, instead of the usual small R and prominent S



A

FIG. 11. A and B. Two patients in whom the transitional zone was displaced unusually far to the left. Lead aV_L in the upper left and Lead aV_F in the lower right indicated that V_6 did not reflect the true left ventricular potential.

wave. Study of aV_F in horizontal hearts and aV_L in vertical hearts often reveals discrepancies that indicate that right ventricular potentials are not reflected by V_1 and V_2 and this fact may be confirmed by leads taken further to the right than the V_1 position.

Case F. H. This case of a 35 year old female (figure 12) is such an example of displaced transitional zone. The patient had cystic disease of the lungs with pulmonary fibrosis. The standard leads revealed a right axis deviation, and in Lead V_1 there was a relatively prominent R with small S (R/S ratio of 4:1). The uni-

polar extremity leads and Lead V_6, however, were not typical of right ventricular hypertrophy.[21, 22, 23, 24] The appearance of Lead aV_L suggests that leads to the right of V_1 may be more representative of right ventricular potentials, and this is confirmed by Leads V_{3R} and V_{1_2}. V_E, which usually reflects right ventricular potentials,

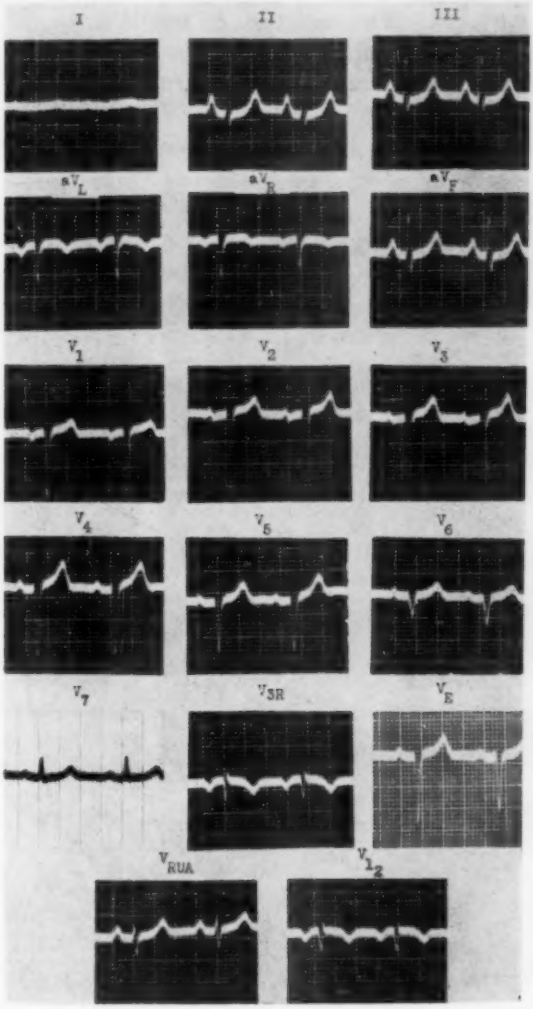


FIG. 11B

resembles V_6 and further supports the opinion that counterclockwise rotation has occurred with displacement of the transitional zone to the right.

One does not always have the opportunity in routine electrocardiography to have the patient return for further leads, and inferences drawn from study of the unipolar extremity leads will prove very helpful in practice.

V. Acute Myocarditis. Occasionally, in patients with myocarditis associated with acute infectious disease, the sole or major abnormalities may be noted in a unipolar extremity lead.[25] In the case of a 19 year old female who had diphtheria (figure 13), serial changes revealed inverted T waves in aV_F which reverted to normal as the myocarditis subsided.

VI. Nodal Rhythm. The direction of the P wave in the left leg lead at times is helpful in determining the origin and spread of the excitation wave. Since normally the impulse passes from the sinus node downward

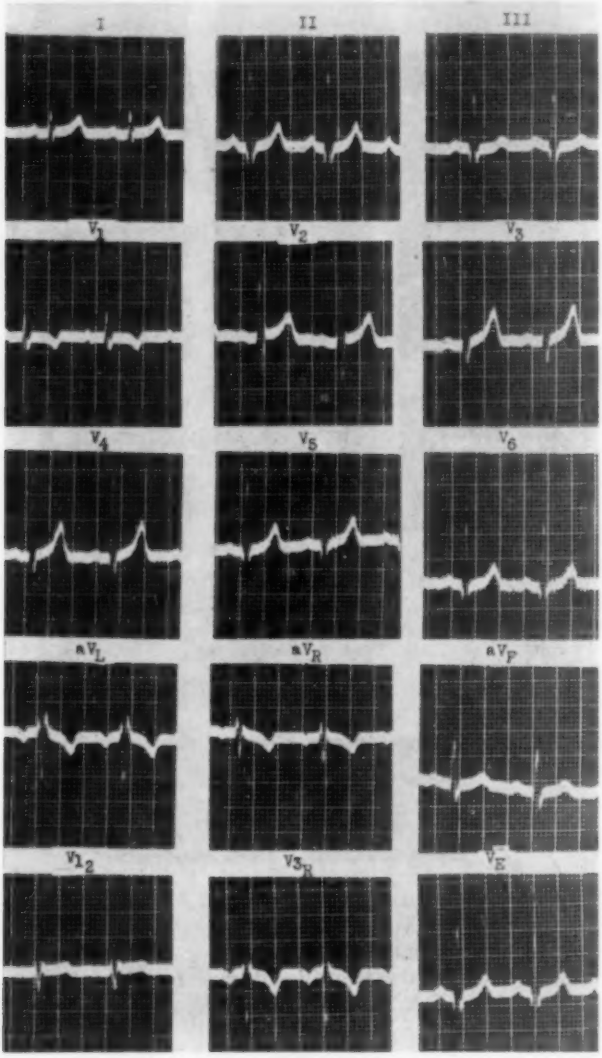


FIG. 12. A patient with displacement of the transitional zone to the right.

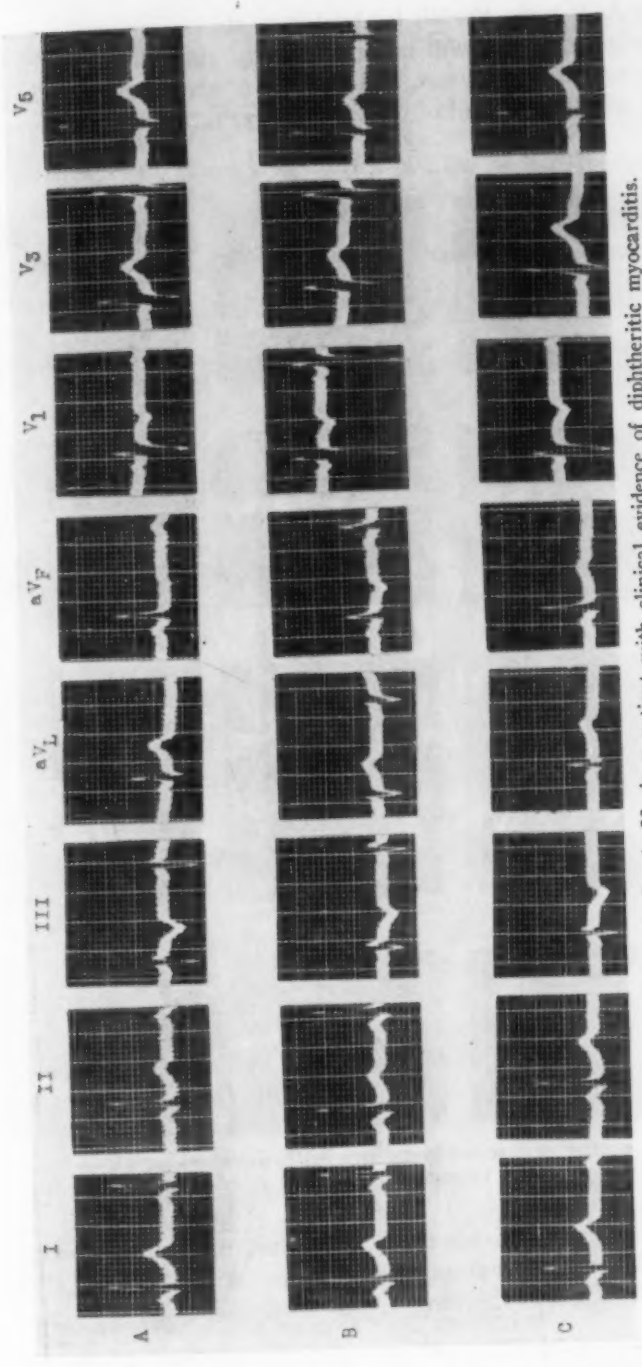


FIG. 13. Serial changes in Lead aV_F in a patient with clinical evidence of diphtheritic myocarditis.

toward the A–V node, the left leg lead faces the oncoming wave of excitation and an upright P wave will be seen. If the impulse arises in or near the A–V node or coronary sinus, and spreads upwards toward the sinus node, the left leg will face the tail of the wave of excitation and an inverted P wave

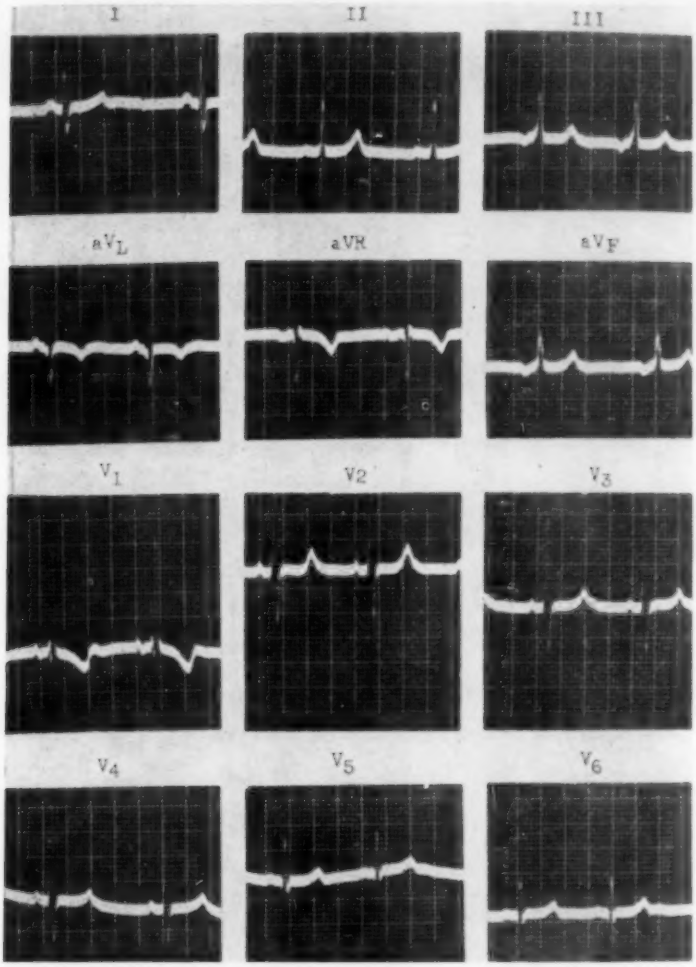


FIG. 14. Nodal rhythm as revealed by an inverted P wave in Lead aV_F. The P–R interval is normal. The patient also has right ventricular hypertrophy.

will result. In some patients the P waves are most clearly seen in the left leg, and an inverted P wave in this lead, even with a normal P–R interval, indicates an A–V nodal rhythm.

Case W. J. W. This 8 year old male (figure 14) is a patient with probable intra-auricular septal defect and right ventricular hypertrophy, and the case illustrates

this abnormality. The P wave is small and diphasic in Lead II and V_6 and inverted in Leads III and aV_F. The P–R interval of 0.10 to 0.12 second is consistent with upper A–V nodal rhythm.

Discussion

It is apparent that unipolar extremity leads at times provide information not obtained from the three standard limb leads or the six routine unipolar precordial leads, V_1 through V_6. After experience with the unipolar leads, one learns to predict what they will reveal after studying the standard limb leads, but direct evaluation of the individual extremity lead is more profitable. The extra time and effort required to record, develop and mount the three unipolar limb leads is worthwhile because of the information that may lead to a correct diagnosis. High anterior or lateral myocardial infarction is the most important of the lesions in which changes in aV_L may be critical. Small lesions not picked up by precordial electrodes may nevertheless be of a size sufficient to produce changes in the left arm lead. It is not clear why in one case with a small lesion, aV_L will be abnormal and yet, in another with clearly abnormal precordial leads over several positions, the left arm lead is normal. Rotational factors undoubtedly play a rôle and the left arm lead may at times reflect most clearly apical, septal or high anterior lesions in individual cases.[7]

It is of interest that the extremity leads such as aV_L reflect changes seen in relatively localized precordial areas. At times, changes in aV_L reflect lateral myocardial abnormalities. At other times aV_L more closely portrays abnormalities arising in the region of the interventricular septum, near the transitional zone. It has not been previously noted in left ventricular hypertrophy that the precordial abnormality might be more definitely seen in left precordial leads from the third or the sixth and seventh interspaces than from the usual fifth interspace leads. One usually thinks of left ventricular hypertrophy occurring in patients with hypertension or aortic valvular disease as involving the entire mass of the left ventricle. However, the importance of initial involvement of the outflow tract of the left ventricle and the position of the diaphragm and of the heart must be considerable. When the heart is horizontally placed in a high position, as in case C. S. (figure 5), the major abnormality was noted in leads from the third interspace. When the heart was placed in a low position, as in case L. G. R. (figure 10), the major abnormalities were noted in the sixth and seventh interspaces. It is of interest that the sixth or seventh interspace, or left posterior leads, may on occasion reveal the source of the abnormality appearing in aV_L or aV_F. Complete exploration of the chest was done in only a few of our cases.

Conclusion

1. The importance of the unipolar extremity leads in providing information over and above that obtained by the routine three standard limb leads and six unipolar precordial leads is discussed and illustrated.

2. Abnormalities in the unipolar extremity leads:

a. May be most characteristic of the particular pattern represented, even though the precordial or standard limb leads may show some abnormalities;

b. May be the sole abnormalities in the 12-lead electrocardiogram;

c. May be less characteristic than the precordial leads.

3. The most important clinical situations in which the unipolar extremity leads may be helpful are as follows:

a. Changes in aV_F may be the sole electrocardiographic abnormalities in posterior myocardial infarction.

b. Relative negativity of the left leg lead in relation to the left arm lead may explain the presence of a Q wave in standard Lead III in the absence of disease.

c. The significant abnormalities in the left arm lead may direct attention to the possibility of a localized anterior or lateral myocardial infarction recent or old; further exploratory precordial leads may then show characteristic abnormalities. In the evolution of anterior myocardial infarction, the earliest signs may appear in the left arm lead.

d. Abnormalities in the left arm lead in horizontal hearts, and in the left leg lead in vertical hearts, may be the earliest or most prominent findings in left ventricular hypertrophy.

e. Inspection of the unipolar extremity leads will permit clearer evaluation of rotation of the heart. At times, study of the unipolar extremity leads will permit the conclusion that the changes in V_6 do not reflect left ventricular potentials, and will indicate the need for further left precordial leads.

f. Myocarditis may be revealed solely by changes in the extremity leads, especially aV_F.

g. P wave is often most clearly seen in aV_F and provides better data on the site of origin of the auricular impulse.

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THE CLINICAL VALUE OF NEEDLE BIOPSY OF THE LIVER *

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The following presentation is based on studies carried out during the past six years, by successive fellows and the author, on the Medical Service and in the Gastric Laboratory of the Cincinnati General Hospital, in collaboration with Dr. Edward A. Gall and his associates of the Department of Pathology of the University of Cincinnati Medical School. Over 700 biopsies have been performed without a fatality, although, according to the recent literature, the mortality is about 0.5 per cent. The biopsy specimens were obtained with the Vim-Silverman needle, the transthoracic approach being used in the great majority of cases. Severe hemorrhage, the chief risk, has occurred once, about six weeks ago. The technic we use and the contraindications we observe have been described elsewhere.[1]

On the basis of our experience, we consider needle biopsy of the liver to be of clinical value in the following nine categories:

I. Excluding Hepatic Disease in the Presence of Suspected Liver Enlargement or Abnormal Liver Function Tests

Hepatic disease is often suspected when the liver is palpable in an individual giving a strong alcoholic history, but needle biopsy of the liver may reveal no abnormalities. Similarly, a palpable liver in a patient with a malignant tumor may wrongly suggest hepatic metastasis. We have become impressed by the frequency with which one can palpate the normal liver one to two fingerbreadths below the right costal margin. Abnormal liver function tests, especially bromsulfalein retention, may be encountered in the absence of clinically significant liver disease, particularly in the presence of fever.[2]

II. Differentiation of "Medical" and "Surgical" Jaundice

In the differentiation of medical and surgical jaundice, my associates and I have found liver biopsy of much greater value than a group of commonly employed liver function tests used individually [3] or in combination.[4] The histologic changes characterizing viral hepatitis have been described by Roholm and Iversen,[5] Dible, McMichael and Sherlock [6] and by Mallory [7];

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while those occurring in obstructive jaundice have been reported by Roholm and Krarup,[8] Popper and Franklin,[9] McMichael[10] and by my associates and me.[4] There may be more difficulty in the biopsy diagnosis of viral hepatitis after the first two weeks of the disease because of the disappearance of the intralobular changes. On the other hand, the biopsy diagnosis of obstructive jaundice is, in our experience, more easily made after two weeks of jaundice.

Needle biopsy of the liver was essential to diagnosis in the following four cases of jaundice:

Case Reports

Case 1. H. G., a 55 year old colored male, was found to have icteric spinal fluid on a routine lumbar puncture done as a follow-up of arsenical therapy administered five or six months before. Because he was colored and had had enucleation of both of his eyes, it was impossible to recognize the icterus clinically or to determine its duration. He complained of anorexia and diarrhea. His liver extended three fingerbreadths below the right costal margin, and his spleen was palpable one fingerbreadth below the left costal margin. The one minute serum bilirubin was 16 mg. per cent, the total bilirubin 30.8 mg. per cent. The cephalin cholesterol flocculation was 3 plus in 24 hours, the thymol turbidity 3, and the serum alkaline phosphatase 11.6 Bodansky units. Because of the history of arsenical therapy and the presence of an enlarged liver and spleen, a diagnosis of homologous serum jaundice was made in spite of the discrepancy in the laboratory findings. Needle biopsy of the liver revealed the changes characteristic of obstructive jaundice, including a "bile-lake" (figure 1). Because of the biopsy findings, we changed our diagnosis to obstructive jaundice and advised surgery. At operation the liver and spleen were enlarged, but there was no distention of the gall-bladder or common bile duct and no tumor was palpable in the region of the ampulla of Vater or head of the pancreas. The surgeon turned to me and said, "I think your original clinical diagnosis of hepatitis is correct." I told him that I would be inclined to agree with him except for the presence of the bile-lake in the biopsy specimen, which we had thus far seen only in extrahepatic obstructive jaundice. I asked him to open the main hepatic duct, which proved to be the site of a carcinoma.

Case 2. A. R., a 39 year old white female, entered the hospital with a complaint of weakness, fatigability, general malaise and epigastric soreness of two weeks' duration. She had been jaundiced for three days. Her liver was tender and extended four fingerbreadths below the right costal margin. The one minute serum bilirubin was 10 mg. per cent, the total 12 mg. per cent. The cephalin cholesterol flocculation was negative, the thymol turbidity 2 units, and the serum alkaline phosphatase 3.4 Bodansky units. Because of the history and physical findings, a diagnosis of viral hepatitis was strongly considered in spite of the discrepancy in the laboratory tests. Needle biopsy of the liver revealed the presence of a metastatic ovarian carcinoma. There had been no suspicion of tumor prior to the biopsy.

Case 3. C. G., a white male, aged 64, entered the hospital with a story of upper abdominal pain and jaundice of about two weeks' duration. His liver was enlarged and tender. The one minute serum bilirubin was 8 mg. per cent, the total bilirubin 12 mg. per cent, the cephalin cholesterol flocculation 4 plus in 24 hours, the thymol turbidity 7, and the serum alkaline phosphatase 5 Bodansky units. The one minute serum bilirubin increased to 22 mg. per cent and the total bilirubin to 36 mg. per cent. The thymol turbidity increased to 23 and the cephalin cholesterol flocculation remained 4 plus in 24 hours. The serum alkaline phosphatase did not exceed 9

Bodansky units. The total blood cholesterol was 150 mg. per cent, with practically no ester fraction. It appeared that we were dealing with a rather severe form of hepatitis. Liver biopsy, however, revealed the presence of cholangitis with some focal necrosis and bile stasis, indicating an entirely unsuspected obstructive jaundice. A common duct stone was subsequently removed at operation.

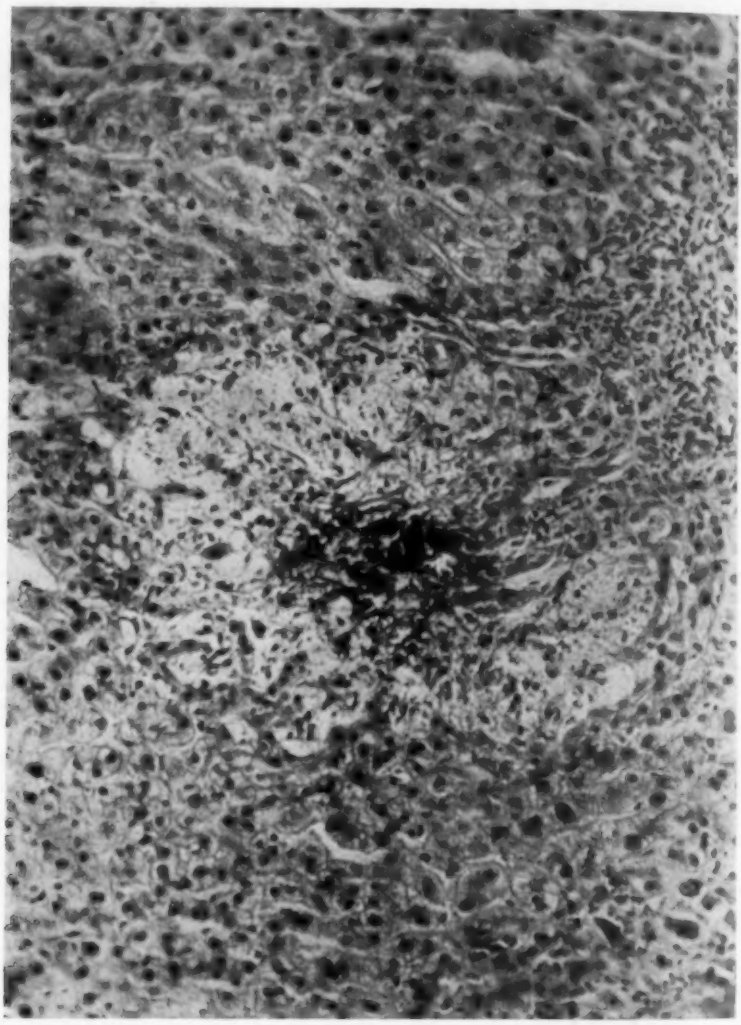

FIG. 1. H. G., obstructive bile stasis. The bile-lake is characterized by a central pool of extravasated bile surrounded by a pale-staining halo of degenerating liver cells with a feathery reticulated appearance.

Case 4. J. K., a 56 year old white male, was admitted to the Jewish Hospital with a history of malaise and weakness of three months' duration, marked anorexia for six weeks, and jaundice for two weeks. He had lost 10 pounds in weight. There was no history of abdominal pain or exposure to known hepatotoxic agents. Physical examination revealed a moderately severe jaundice but was otherwise not remarkable.

The cephalin cholesterol flocculation was negative, thymol turbidity 7.4 units, the one minute serum bilirubin 7.8 mg. per cent, the total bilirubin 10.1 mg. per cent, serum alkaline phosphatase 13.7 Bodansky units, the total blood cholesterol 740 mg. per cent, and the ester fraction 355 mg. per cent. The clinical and laboratory findings, except

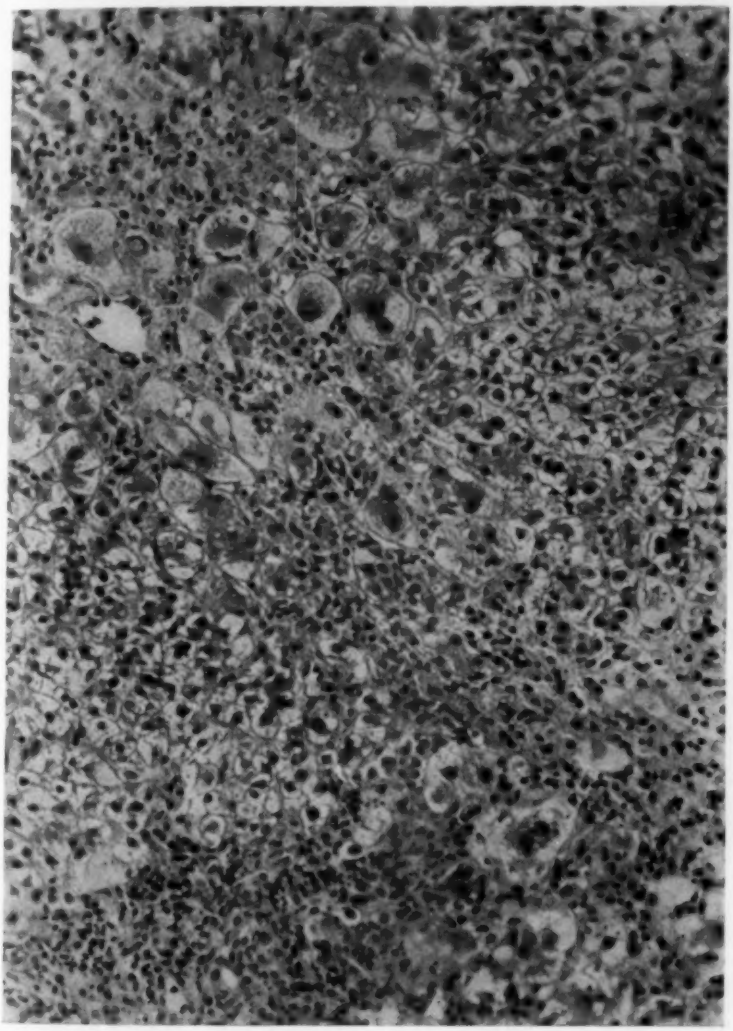

FIG. 2. G. C., viral hepatitis, acute. The portal area is the seat of an intense infiltration with lymphocytes. Many isolated foci of unicellular necrosis are present, and there is a striking mass of parenchymatous cells exhibiting balloon-like swelling and nuclear reduplication.

for the slightly increased thymol turbidity, were in favor of extrahepatic obstructive jaundice. An operation had been advised by several consultants who saw the patient. Liver biopsy revealed the pericholangitic phase of viral hepatitis. Operation was accordingly deferred and the patient made a complete recovery.

III. Observation of the Natural Course of Liver Disease

Liver biopsies afford the best means of ascertaining the disappearance of hepatitis or the development of chronic hepatitis or cirrhosis. Volwiler and Elliott [11] have studied the late manifestations of epidemic infectious hepatitis by means of needle biopsy of the liver.

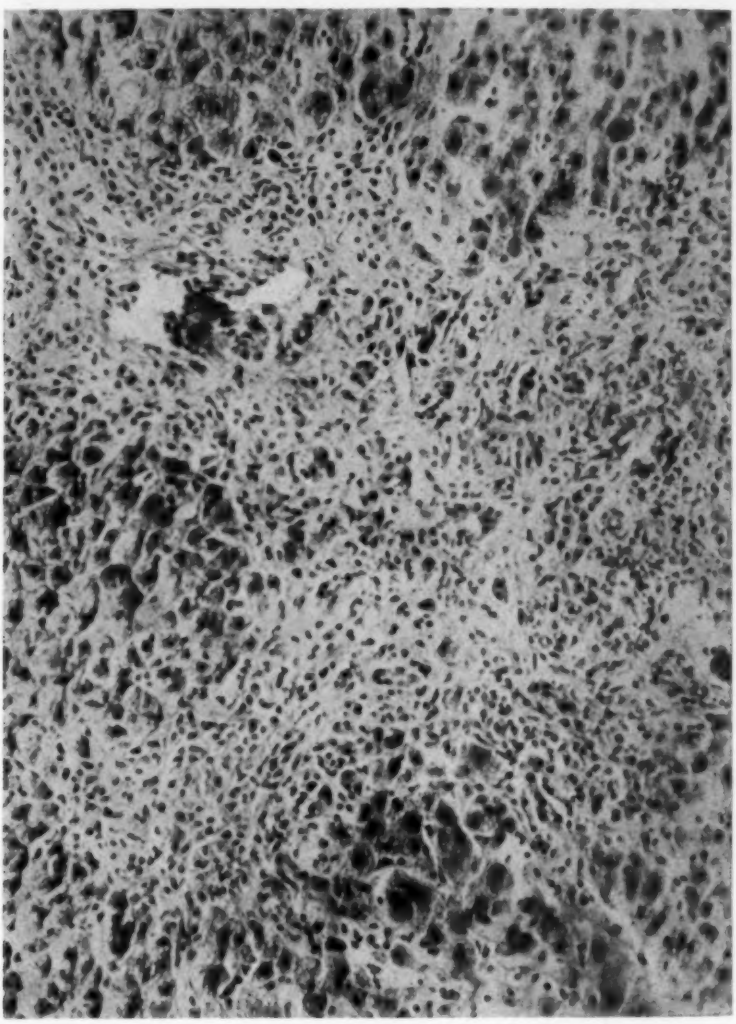

Fig. 3. G. C., subacute viral hepatitis. The section is prepared in different fashion from the preceding one (acetone fixation). It is difficult, therefore, to compare the two with respect to cytologic detail, although the cells exhibit similar features. The photograph exhibits a large area of portal fibrosis resulting from loss of lobular substance. There is increase in the number of biliary radicles, and the lymphocytic triaditis continues unabated.

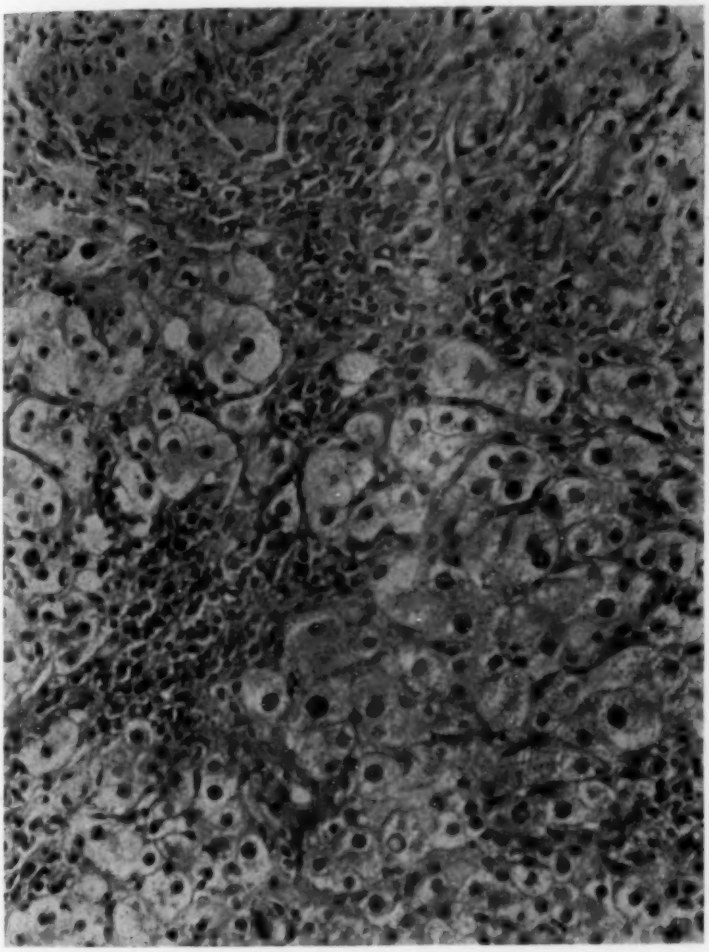

FIG. 4. A. I., miliary granuloma in a case of sarcoidosis. Lobular architecture is distorted by irregular strands of fibrous tissue infiltrated by lymphocytes and plasma cells. At one edge, the margin of a tubercle containing two giant cells may be seen.

Case 5. G. C., a 63 year old white male, had homologous serum hepatitis with typical changes in a biopsy specimen obtained on the sixteenth day of jaundice (figure 2). On the thirty-ninth day of jaundice a second biopsy showed considerable fibrosis, which was interpreted as a possible postnecrotic cirrhosis (figure 3). It is, of course, possible that the first biopsy may have failed to reveal an existing fibrosis. Like Krarup,[12] we believe that the transition of hepatitis into cirrhosis may occur rather rapidly, although, admittedly, histologic changes like those of this patient may be construed as fibrosis rather than cirrhosis.

Figure 4 shows the biopsy obtained from a patient with sarcoidosis and reveals scattered granulomas. A biopsy made 10 months later shows fibrosis in addition to the sarcoidosis (figure 5). A relationship between

the two diseases is suggested but of course not proved by these observations. It is Dr. Gall's belief that the second biopsy reveals an early postnecrotic cirrhosis. The relationship between granulomatous disease and cirrhosis has been strongly hinted at in the literature, at least in the case of brucellosis.[13, 14]

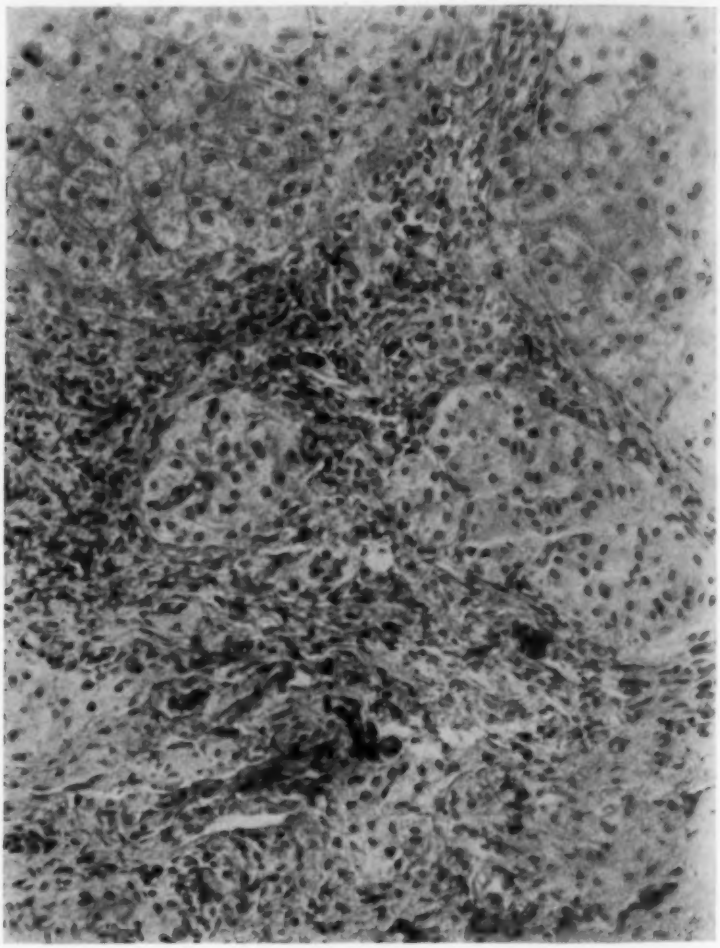

FIG. 5. A. I., same case as figure 4, 10 months later. Fibrosis is prominent and there is not a well-defined micronodular structure. Although inflammatory cells persist, tubercles are no longer evident in this specimen.

IV. Evaluation of Therapy of Liver Disease

The importance of liver biopsy in the evaluation of therapy in liver disease has been stressed by Volwiler and Jones [15] and by Volwiler, Jones and Mallory.[16]

Case 6. Figure 6 illustrates the biopsy obtained from an obese female of 55 years who is nonalcoholic but who ingests too little protein. It reveals extensive fatty vacuolization of the liver. In addition to an adequate diet, she was given 4 gm. choline * daily for six months, and biopsies showed no change in the degree of fatty

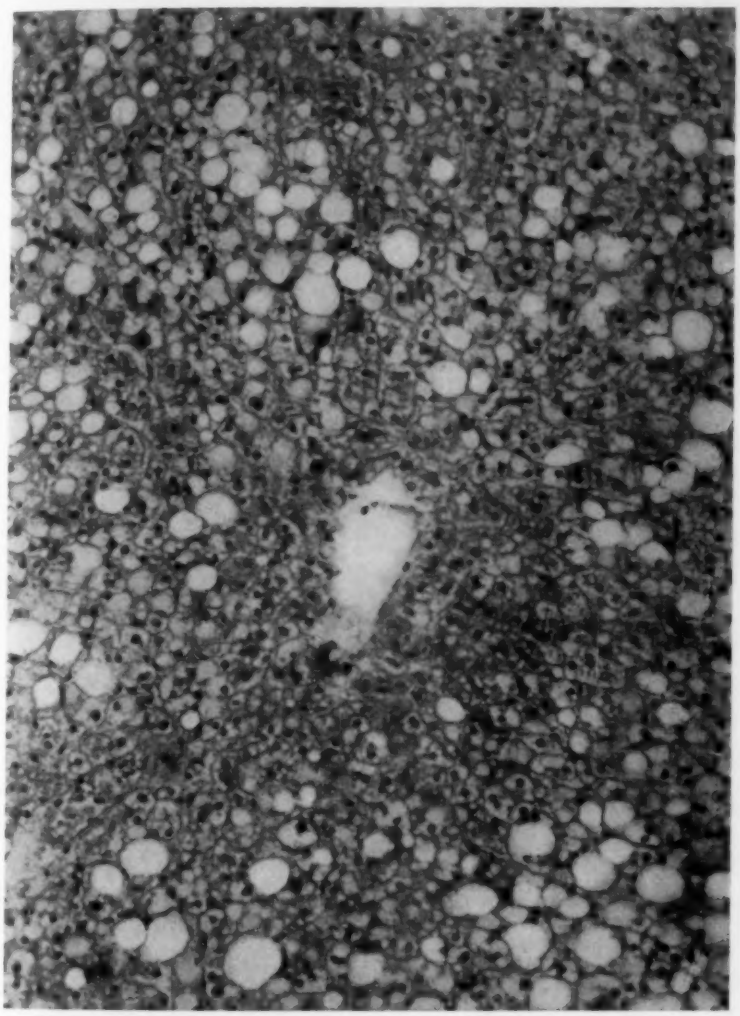

FIG. 6. J. M., severe fatty vacuolization. A severe grade of parenchymatous vacuolization with no evidence of liver cell necrosis.

vacuolization at either three months or six months. The dosage of choline was increased to 16 gm. a day, and a biopsy four months later showed a marked decrease in the amount of fatty vacuolization (figure 7). The dose of choline was then

* Syrup of choline dihydrogen citrate was kindly supplied by Flint Eaton & Co., Decatur, Illinois.

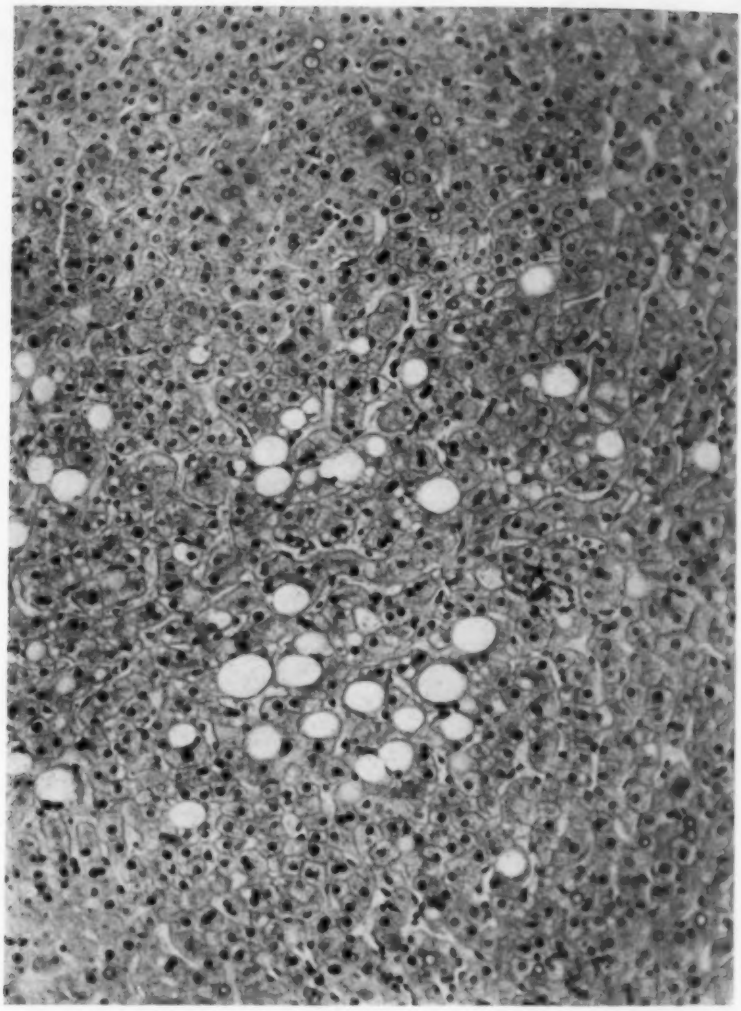

FIG. 7. J. M., same patient (figure 6), 10 months later. There is a striking reduction in the amount of fatty vacuolization. Liver cells show no evidence of distortion or disintegration.

dropped to 4 gm. a day, and three months later biopsy revealed marked increase in the degree of fatty vacuolization. During a period of a little over three years, this patient has shown no evidence of the development of cirrhosis in the biopsy specimens.

V. Demonstration of the Histologic Phase of the Liver Disease Present and Elucidation of the Cause of Hepatomegaly

Volwiler, Jones and Mallory [16] made the following statement, which our experience has repeatedly confirmed: "The most careful clinical scrutiny of the patient with any chronic hepatitis may not permit one to predict with

even moderate accuracy the histologic phase of the liver disease present. Neither do any known laboratory tests of hepatic function, even when repeated serially, always correctly reflect the true histologic statement at a given time, or the changes taking place during clinical observation; frequently the only means of determining this is microscopic examination of actual liver tissue."

The following two cases illustrate the value of liver biopsy in revealing the true nature of an hepatomegaly.

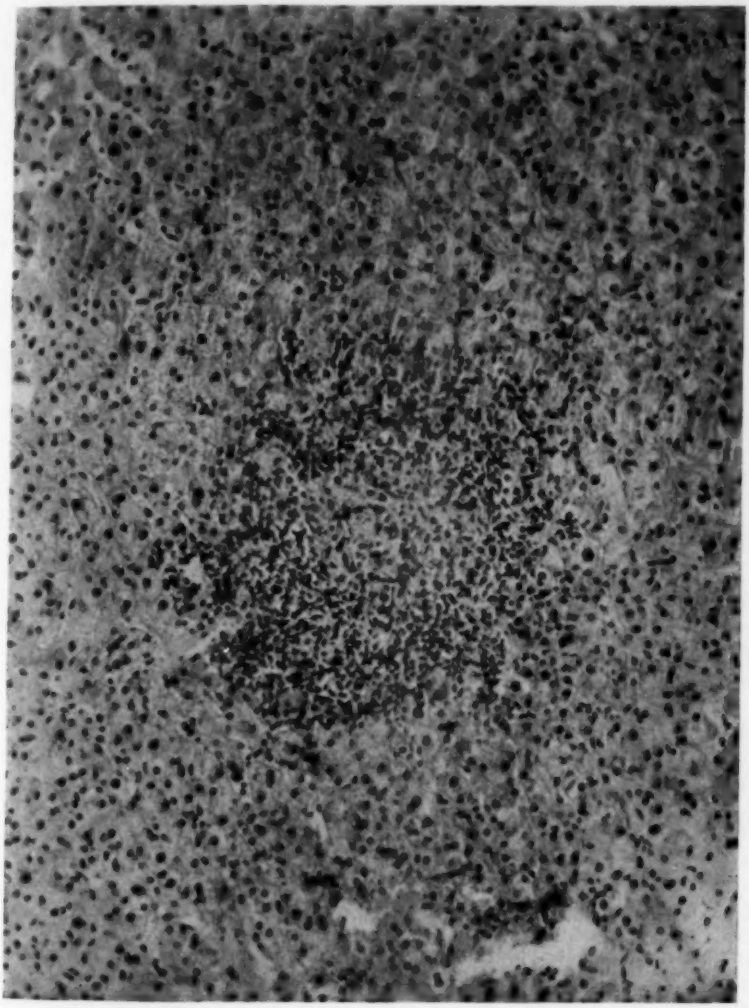

FIG. 8. W. R., miliary granuloma. A circumscribed inflammatory nodule with an outer rim of lymphocytes and plasma cells and a central core of histiocytes. The latter are not arrayed concentrically, and there is evidence of neither necrosis nor giant cell formation. The surrounding liver substance is unremarkable.

Case 7. W. R., a colored male of 35 years, had had epigastric pain following meals for about eight months. Relief of pain frequently followed vomiting. There was a history of tarry stools and weight loss. The liver extended three fingerbreadths below the right costal margin and a mass was palpable in the upper abdomen. Roentgenologic examination revealed evidence of external compression of the distal stomach

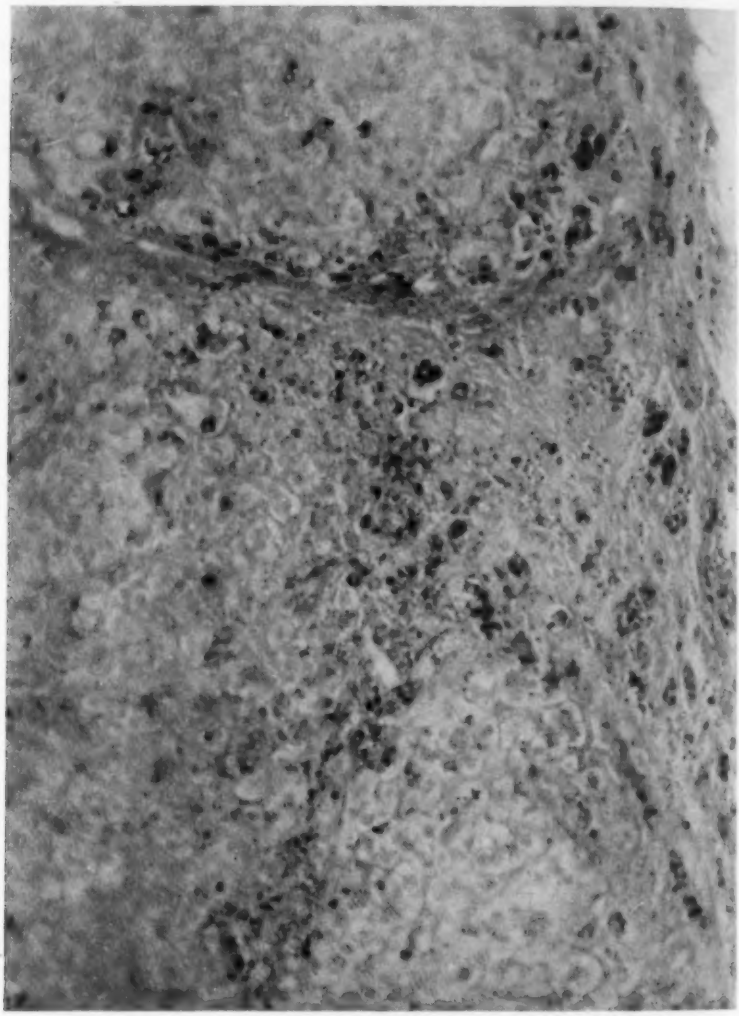

FIG. 9. M. L., hemochromatosis with pigmenting cirrhosis. This specimen, stained to demonstrate iron pigment, reveals dark staining hemosiderin in particular abundance with a strand of fibrous tissue. It appears to a less well marked degree in parenchymatous cells.

and duodenum, due probably to neoplasm. The liver profile was entirely normal. The clinical diagnosis was intraabdominal neoplasm with probable hepatic metastases. Liver biopsy revealed the presence of tubercles (figure 8), and led to a diagnosis of intraabdominal tuberculosis, which was verified by lymph node biopsy obtained at

laparotomy. There had been no suspicion of a granulomatous disease before the biopsy was performed.

Case 8. M. L., a 72 year old white male, was admitted to the hospital with a three weeks' history of weakness and vague abdominal pain and a two weeks' history of abdominal swelling and ankle edema. There was no history of alcoholism. Physical examination revealed tanning of the skin, slight icterus, a nontender liver extending two fingerbreadths below the right costal margin, a palpable spleen and ascites. The cephalin cholesterol flocculation was 3 plus in 24 hours, the thymol turbidity 19, the one minute serum bilirubin 0.8 and the total bilirubin 3 mg. per cent. The glucose tolerance test was normal and there was no glycosuria. A skin biopsy was negative for evidence of hemochromatosis. Although no tumor cells were demonstrated in the ascitic fluid, the rapid downward course and the constant abdominal pain with increasing weakness suggested the diagnosis of intraabdominal malignancy with liver metastases or the possibility of hepatoma superimposed upon cirrhosis. The liver biopsy revealed the presence of hemochromatosis, which was verified at necropsy (figure 9).

VI. Elucidation of the Hepatosplenopathies

Case 9. B. W., a 20 year old white male, complained of vague illness for 11 months. He had lost 20 pounds in weight and had had itching of the skin. Three months before admission he was found to have an enlarged liver and spleen. At the time he was admitted to the Christian R. Holmes Hospital his liver extended four fingerbreadths below the right costal margin and his spleen two fingerbreadths below the left costal margin. There was slight enlargement of inguinal lymph nodes but there was otherwise no peripheral lymphadenopathy. The cephalin cholesterol flocculation was 4 plus in 24 hours, the thymol turbidity 8 units, the one minute serum bilirubin 0.1 mg. per cent and the total bilirubin 0.4 mg. per cent. A clinical diagnosis of Hodgkin's disease was entertained. Liver biopsy revealed the presence of miliary granulomas with suggestive Schaumann or pre-Schaumann bodies (figure 10). This led to the clinical diagnosis of sarcoidosis, with which the patient's course has proved quite compatible. A lymph node biopsy revealed the same changes as the liver biopsy.

Case 10. J. D., a 24 year old white male, entered the hospital with complaints of weakness, anorexia, nausea, cramping abdominal pain, chills and fever of one month's duration. The liver extended four fingerbreadths below the right costal margin and the spleen three fingerbreadths below the left costal margin. He had a marked leukopenia, the white blood cells numbering 1,100, with 69 per cent polymorphonuclears. The cephalin cholesterol flocculation was 3 plus in 24 hours, thymol turbidity 4 units, one minute bilirubin 0.1 mg. per cent and total bilirubin 0.6 mg. per cent. A clinical diagnosis of possible typhoid fever was made. There was no peripheral lymphadenopathy. Liver biopsy revealed the presence of granulomas, with cells suggestive of the Reed-Sternberg type. The diagnosis of Hodgkin's disease was verified a month later, when large inguinal nodes were discovered and biopsied.

In the case of J. P., a liver biopsy (figure 11) revealed distention of the liver sinusoids with leukemic cells and proved to be the first confirmatory evidence of a clinical diagnosis of aleukemic leukemia. The bone marrow biopsy had been unsatisfactory.

VII. Differentiation of Extrahepatic and Intrahepatic Block

Distinction between extrahepatic and intrahepatic block is of practical importance to the surgeon contemplating a venous anastomotic operation for

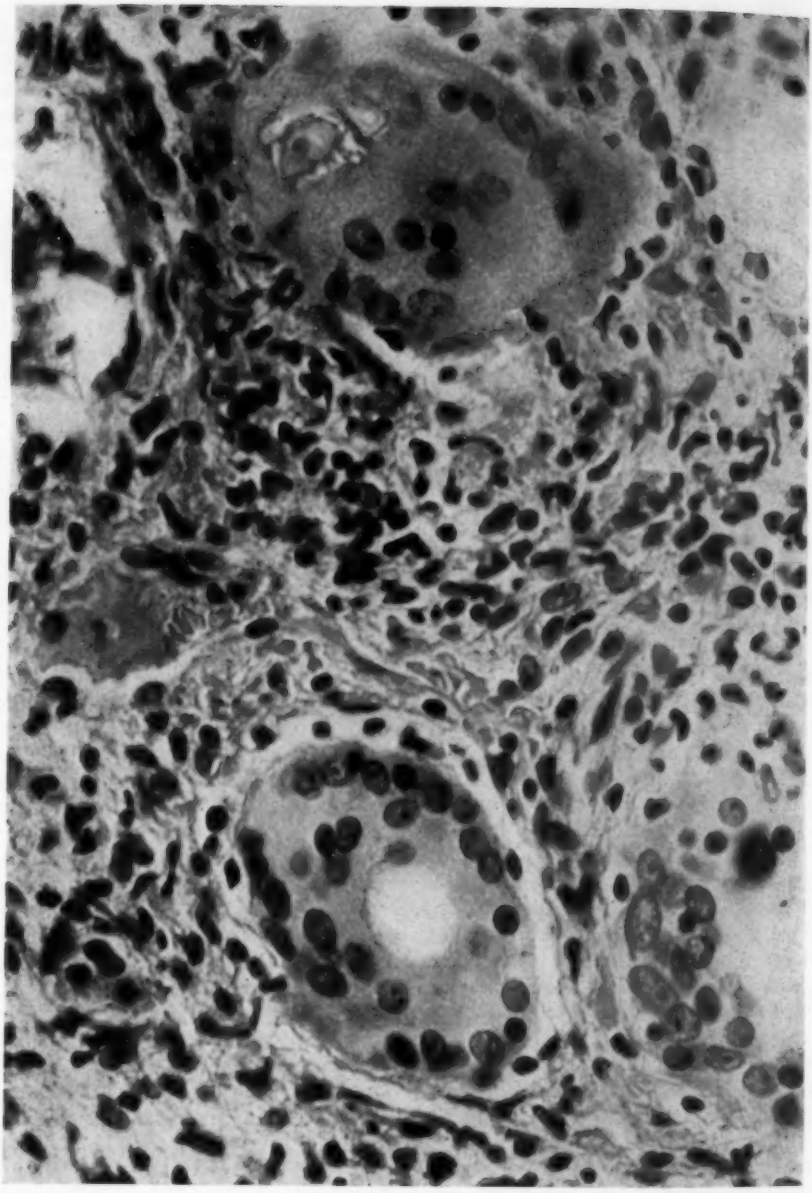

FIG. 10. B. W., miliary granuloma. A high power view demonstrating a pleomorphic nonepithelioid exudate and several of the giant cells containing vacuoles and inclusions of nondescript character.

the relief of portal hypertension. Prognosis is generally more favorable in the extrahepatic form. Porto-caval shunt is to be preferred to spleno-renal anastomosis in the intrahepatic form, while the converse obtains in the extrahepatic variety.

Case 11. A 15 year old white female was admitted with hematemesis. There was a history of previous hematemesis at the age of eight. Her spleen was firm and extended five fingerbreadths below the left costal margin. There was no demonstrable hepatic enlargement. The one minute serum bilirubin was 0.2 mg. per cent and the total bilirubin 1.2 mg. per cent. The cephalin cholesterol flocculation was 4 plus in 24 hours, the thymol turbidity 4, the zinc sulfate turbidity 20, and the serum alkaline phosphatase 2 Bodansky units. There was 8 per cent retention of bromsulfalein 45 minutes after the intravenous injection of 5 mg. of dye per kilogram of body weight. The clinical diagnosis was congestive splenomegaly (Banti's syndrome), with the laboratory findings, though not altogether consistent, suggesting

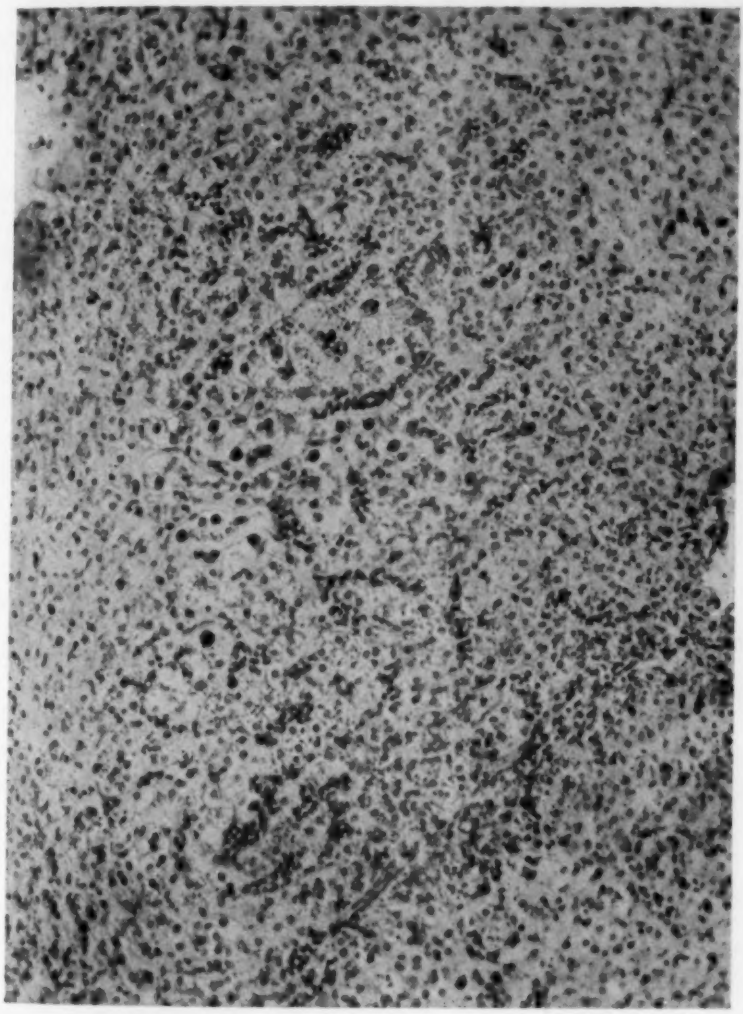

FIG. 11. J. P., lymphocytic leukemia. Many sinusoids are filled with large masses of lymphoid cells. Parenchymatous elements are preserved in orderly arrangement but within a fine deposit of hemosiderin, which is not well shown in the illustration.

intrahepatic block. Liver biopsy, however, was entirely normal, and at laparotomy an arteriovenous aneurysm was found between the splenic vein and splenic artery.

VIII. The Diagnosis of Granulomatous Disease

Giant cells were found scattered throughout the liver biopsy specimen of a patient with miliary tuberculosis who had no enlargement of the liver and who raised no sputum. The liver biopsy furnished the first confirmatory evidence of a tuberculous etiology (figure 12).

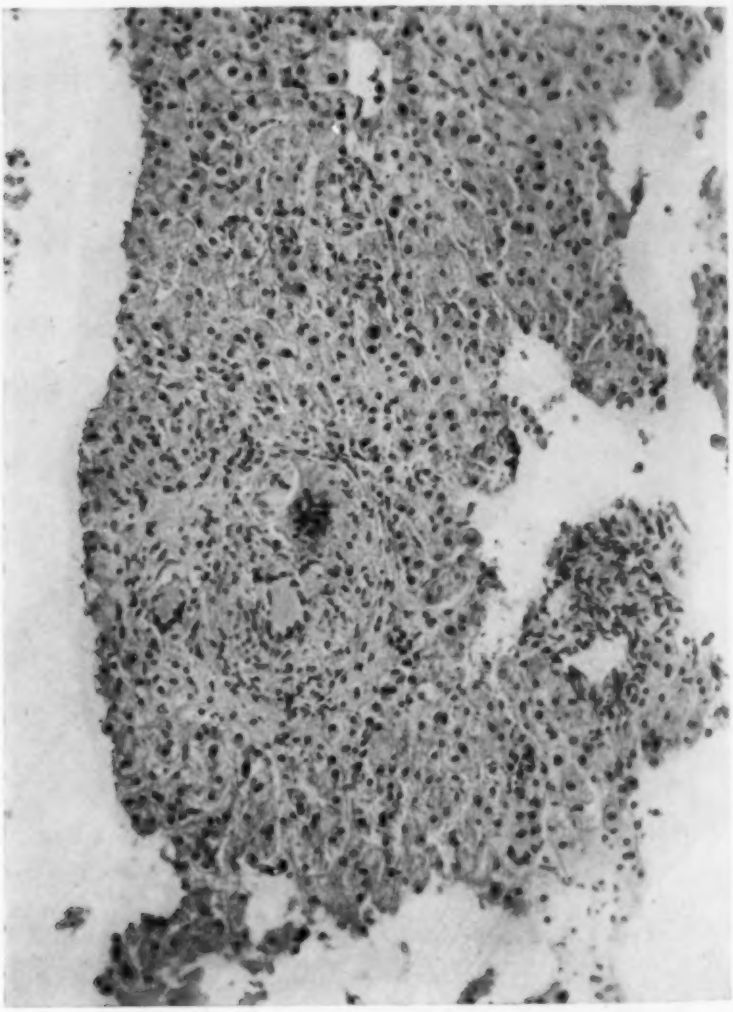

Fig. 12. Y. N., miliary tubercle. Fragmented liver tissue containing a tubercle comprised of concentrically arrayed epithelioid cells. In and about the nodule are several multinucleated giant cells, two of which have the appearance of Langhans' cells.

Granulomatous lesions are frequently present in the livers of patients with brucellosis.[13, 14] Spink and his associates and Cazal have well described these lesions, with their central zone of epithelioid cells and peripheral zone of lymphocytes. Spink et al. could not culture the organism in four instances from portions of the biopsied material. Our experience confirms that of Spink and his associates, in that granulomatous lesions may be present in the liver without obvious hepatic enlargement and without alterations in liver function tests.

We have seen granulomas in the livers of patients with tularemia and secondary syphilis.

Granulomatous lesions have been described in liver biopsy specimens obtained from patients with sarcoidosis.[17, 18, 19] Van Buchem [18] described typical lesions in 11 of 14 patients. Scadding and Sherlock [19] have emphasized the importance of cutting serial sections of the biopsy specimen if the first section shows no lesion, as the lesions are often small and scattered.

Dr. Gall shares the opinion of other pathologists that these granulomatous lesions are not necessarily specific. Thus it may be impossible to differentiate the granulomas of brucellosis, sarcoidosis, tuberculosis, syphilis and nonspecific granulomatous disorders. The chief value of needle biopsy of the liver in this connection is in calling the presence of a granulomatous process to the attention of the clinician. It is then up to him to define the character of the granulomatous lesion, if possible, with the help of additional clinical and laboratory data.

IX. Verification or Detection of Neoplasm of the Liver

We have been quite surprised to learn how often needle biopsy of the liver may reveal the presence of neoplasm. For example, in 53 cases of proved neoplasm which we have reported previously,[20] the liver biopsy demonstrated tumor in 41. In five instances a second puncture—and in one instance a third puncture—was necessary to show the presence of tumor. It is of interest that a positive biopsy was relatively no more frequent in the 33 cases in which the liver was palpated as nodular than in the 18 cases in which it was palpated as smooth. It seemed to make no difference in the end result whether the transthoracic or abdominal approach was used to obtain the biopsy specimen. Ironically enough, occasionally there may be much difficulty in demonstrating the presence of tumor by means of biopsy in a grossly nodular liver obviously the site of neoplasm.

Discussion

A review of 574 needle biopsies of the liver obtained in 500 patients shows that the clinical diagnosis was confirmed in 249 patients, or 49.8 per cent; an erroneous clinical diagnosis was corrected in 98 patients, or 19.6 per cent; and unsuspected disease was revealed in 12 patients, or 2.4 per cent, making a total of 359 patients, or 71.8 per cent, in whom the biopsy

proved a positive aid in diagnosis (table 1). In 141 patients, or 28.2 per cent, the biopsy proved no aid in diagnosis (table 2). For the 249 patients in whom the biopsy proved a positive aid in diagnosis, the clinical diagnoses are listed in table 3. The erroneous clinical diagnoses and the subsequent biopsy diagnoses in the 98 cases included in table 1 are presented in detail in tables 4, 5, 6, 7 and 8. The 12 cases in which biopsy led to the diagnosis of unsuspected disease are listed in table 9.

TABLE I

Clinical Evaluation of Liver Biopsy
(500 Patients; 574 Biopsies)
Positive aid in diagnosis

	No. Patients	Per Cent
Clinical diagnosis confirmed	249	49.8
Clinical diagnosis corrected	98	19.6
Unsuspected disease detected	12	2.4
Total	359	71.8

TABLE II

Clinical Evaluation of Liver Biopsy
(500 Patients; 574 Biopsies)
No aid in diagnosis

	No. Patients	Per Cent
Biopsy noncontributory	92	18.4
Biopsy misleading	15	3.0
Specimen inadequate	34	6.8*
Total	141	28.2

* Actual percentage of failures based on 700 biopsies is 4.8 per cent.

TABLE III

Confirmation of Clinical Diagnosis as Result of Biopsy
(249 Patients)

Clinical Diagnosis	No. of Patients
Cirrhosis	92
Hepatitis	70
Neoplasm of liver	35
Obstructive jaundice	27
Granulomatous disease	8
Fatty vacuolization	7
Miscellaneous	10

TABLE IV

Change in Clinical Diagnosis as Result of Biopsy

Clinical Diagnosis	Biopsy Diagnosis	No. Patients
Nutritional or postnecrotic cirrhosis	Fatty vacuolization	22
	Normal liver	11
	Hepatitis	4
	Neoplasm	3
	Biliary cirrhosis	5
	Obstructive jaundice	1
Total		46

TABLE V

Change in Clinical Diagnosis as Result of Biopsy

Clinical Diagnosis	Biopsy Diagnosis	No. Patients
Metastatic neoplasm	Cirrhosis	6
	Obstructive jaundice	3
	Primary tumor	2
	Fatty liver	2
	Hemochromatosis	1
	Hepatitis	1
	Normal liver	1
Total		16

TABLE VI

Change in Clinical Diagnosis as Result of Biopsy

Clinical Diagnosis	Biopsy Diagnosis	No. Patients
Hepatitis	Cirrhosis	5
	Obstructive jaundice	3
	Metastatic neoplasm	1
	Hemosiderosis	1
	Fatty liver	1
Total		11

TABLE VII

Change in Clinical Diagnosis as Result of Biopsy

Clinical Diagnosis	Biopsy Diagnosis	No. Patients
Obstructive jaundice	Hepatitis	7
	Fatty vacuolization	1
	Nutr. cirrhosis	1
Total		9

TABLE VIII

Change in Clinical Diagnosis as Result of Biopsy
(Miscellaneous Disorders)

Clinical Diagnosis	Biopsy Diagnosis	No. Patients
Fatty liver	Normal liver	3
Hemochromatosis	Cirrhosis	3
Hepatoma	Metastatic neoplasm	2
Abd. neoplasm	Tuberculosis	2
Suspected liver disease	Normal liver	3
Fever unknown origin	Nonviral hepatitis	3
Total		16

TABLE IX

Biopsy Led to Unsuspected Diagnosis
(12 Patients)

Diagnosis	No. Patients
Granulomatous disease	5
Cirrhosis	5
Histiocytosis (nonlipoid)	1
Leukemia	1

TABLE X

Diagnostic Value of Liver Biopsy

Final Diagnosis	No. Patients	Clin. Diag. Incorrect (Biopsy Positive)	Per Cent
Cirrhosis	112	20	17.9
Hepatitis	82	12	14.6
Neoplasm of liver	41	4	9.8
Obstructive jaundice	34	7	20.6

Looking at the diagnostic value of liver biopsy from another angle, it is seen from table 10 that the clinical diagnosis was incorrect and the biopsy positive in 20 (or 17.9 per cent) of 112 patients with cirrhosis, in 12 (or 14.6 per cent) of 82 patients with hepatitis, in four (or 9.8 per cent) of 41 cases of neoplasm of the liver, and in seven (or 20.6 per cent) of 34 cases of obstructive jaundice.

CONCLUSION

At the Cincinnati General Hospital, needle biopsy of the liver has proved of great value in the nine categories discussed. When it is performed by physicians trained in the procedure, with the patients carefully selected and kept in bed under close observation for at least 24 hours afterwards, and transfused if necessary, needle biopsy of the liver entails very little risk. As a result of the biopsy, needless surgery may be averted or earlier operation invoked, advantages which of themselves would well outweigh the risk entailed.

Needle biopsy of the liver should be performed by one or two members of a given hospital staff, to provide the advantages of increasing experience. The diagnostic value of the procedure rises with the growing interest and experience of the collaborating pathologist, as well as the person or persons performing the biopsies.

Acknowledgment: I am grateful to the following fellows and former fellows of the Gastric Laboratory of the Cincinnati General Hospital who have assisted in the studies on which these remarks are based: H. Harold Steinberg, William Molle, Carl W. Kumpe, Stuart A. Safdi, Robert C. Cogswell, Ferdinand G. Weisbrod, Jerome R. Berman and Herman Ulevitch. I am particularly indebted to Dr. E. A. Gall, head of the Department of Pathology of the Cincinnati General Hospital and University of Cincinnati Medical School, for his constant help and coöperation, and to his associates, Daniel F. Richfield, Frank P. Cleveland and Ernest L. Abernathy. I want to thank Dr. Herman Ulevitch for his assistance in the compilation of the statistics used in this paper.

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"ALVEOLAR-CELL" CARCINOMA OF THE LUNG*

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CONSIDERABLE interest has been aroused in a group of pulmonary neoplasms thought to originate in the lining cells of the alveoli. This interest is stimulated by their alleged rarity, and the morphologic and histologic controversy concerning their origin. They are distinguished from other pulmonary neoplasms by a regular layer of nonciliated, cuboidal to low columnar cells which line the alveoli, and by the absence of evidence of primary bronchial involvement.

Two cases are presented as examples of alveolar-cell carcinoma.

CASE REPORTS

Case 1. A 60 year old Italian-born male was admitted to The New York Hospital complaining of increasing dyspnea and cough of 14 months' duration. For 37 years, as a frame finisher, he had applied a composition of tar, linseed oil, glycerin and glue to picture frames.

Present Illness: About 14 months prior to admission, he noted the onset of mild cough productive of small amounts of white, frothy, nonbloody sputum. Three months later, a complaint of epigastric distress led to a roentgen-ray examination of the gastrointestinal tract, which revealed no abnormality but disclosed densities in both lungs.

This discovery led to admission to a local hospital where, except for evidence of weight loss, physical examination was recorded as being unremarkable. Chest roentgenograms revealed numerous bilateral parenchymal deposits, interpreted variously as inflammatory condition, pneumoconiosis, metastatic carcinoma and Boeck's sarcoid. During the 11 months following discharge, dyspnea and frequency of cough increased. On serial roentgen-ray examinations, the multiple densities appeared to become confluent, sparing the periphery and hilar areas.

Because of dyspnea and severe paroxysmal coughing, he was admitted to this hospital. Physical examination revealed an emaciated, dyspneic, slightly cyanotic male with a cough productive of nonbloody, clear, thin, frothy sputum. There were dullness to percussion in the right axillary area, moist expiratory râles over the right anterior chest, and scattered rhonchi over the right posterior base. Hemoglobin was elevated to 19.0 gm. and the red blood cell count to 7.3 million. Temperature, white blood cell and differential count, and blood chemistry studies were within normal limits. A chest roentgenogram (figure 1) revealed deviation of the mediastinum and trachea to the right, and a diffuse, mottled infiltrate extending peripherally from the central lung fields. The films were interpreted as bronchiogenic carcinoma, with an added note, however, that the changes were compatible with those seen in Boeck's sarcoid, pulmonary tuberculosis, metastatic carcinoma or fungus infection.

His temperature became elevated to 39° C. (102.2° F.) on the second hospital day and remained elevated as the patient pursued a rapid downward course. Search for a possible extrapulmonary, primary neoplastic site was fruitless. On the twelfth hospital day dyspnea and cyanosis suddenly became more marked, as a spontaneous

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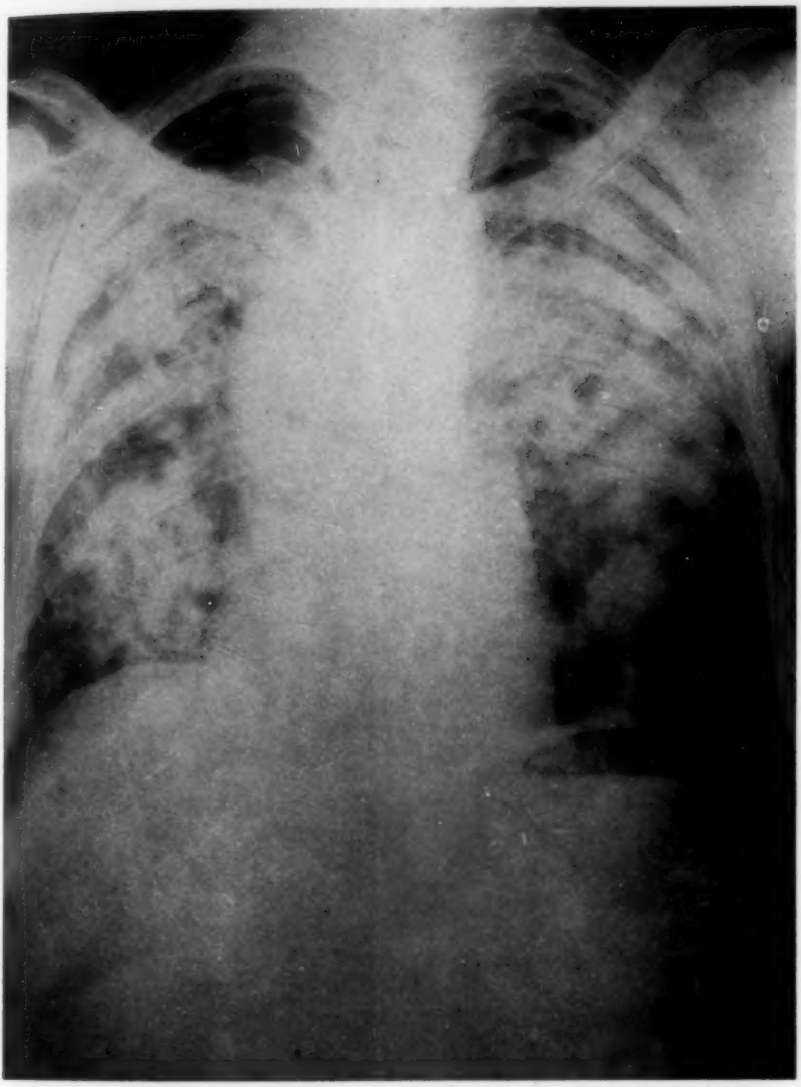

FIG. 1. *Case 1.* Chest roentgenogram shows deviation of the mediastinum and trachea to the right, and a diffuse, mottled infiltrate extending peripherally from the central lung fields.

pneumothorax had occurred on the right. He died in respiratory distress on the sixteenth hospital day.

Postmortem Examination: * Five hundred centimeters of clear, pale yellow fluid were found in the left pleural cavity, and a pneumothorax with a few cubic centimeters of similar fluid on the right. Together the lungs weighed 2,000 gm. On cut section, all lobes presented a firm, gray-white appearance except at the periphery,

* Autopsy performed by Dr. John B. Graham.

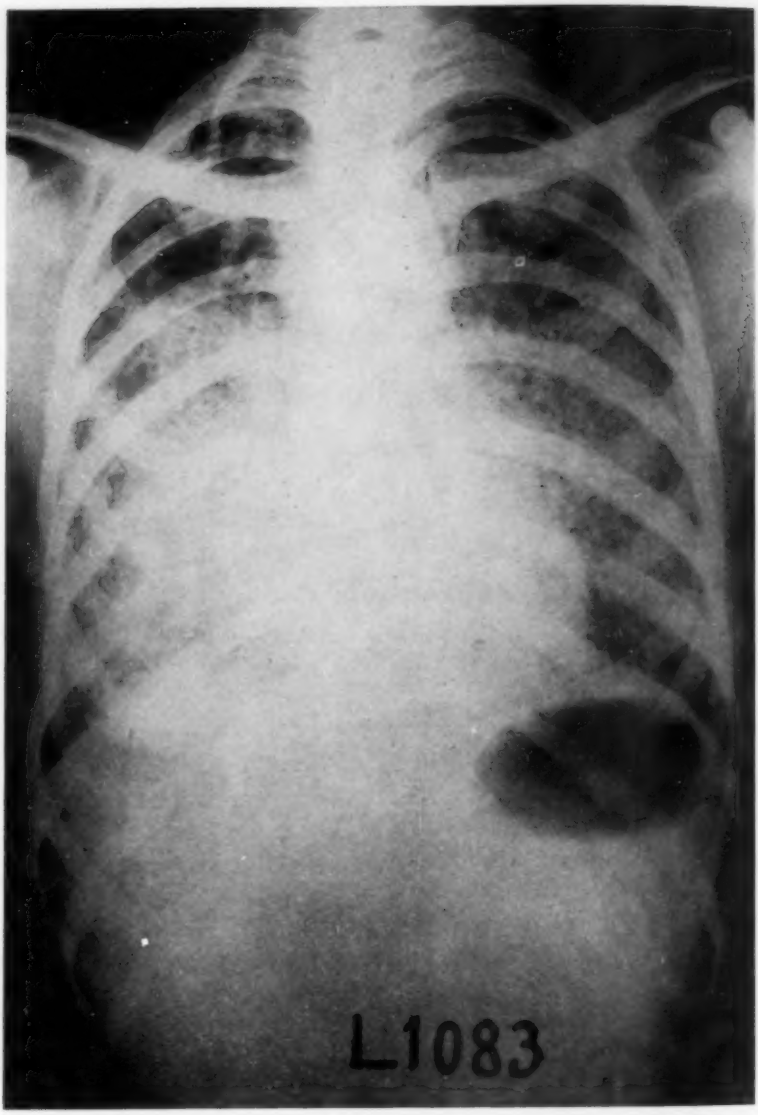

FIG. 2. *Case 2.* Chest roentgenogram reveals a diffuse mottling throughout both lungs, most dense in the hilar areas and radiating well out into the periphery.

where there was a 5 to 10 mm. margin of fairly normal appearing crepitant lung. Bronchial ramifications were carefully examined for tumor masses and none was found. The tracheobronchial lymph nodes and liver contained a few discrete, gray-white nodules. Microscopic examination will be described with that of the next case.

Case 2. A 31 year old Italian-born American housewife was admitted to The New York Hospital complaining of increasing shortness of breath of six weeks' duration. Her past history included no significant illnesses. At the age of 17 she was in contact with a sister who developed active tuberculosis. Employed in a

textile house for several years in her early twenties, she patted a fine white powder into fabrics with a blackboard eraser. She wore no mask and was frequently heavily covered with this fine dust, composed of zinc oxide and rosin.

Present Illness: Six weeks prior to admission she noted the onset of dyspnea on exertion, fatigue and a mild nonproductive cough. These symptoms progressed and were accompanied by an eight pound weight loss. One week prior to admission, a Board of Health roentgenogram was interpreted as resembling miliary tuberculosis, and she was referred to this hospital as a candidate for streptomycin therapy.

Physical examination revealed a small, thin, poorly developed white female who was dyspneic on exertion. She was afebrile and had a dry, hacking, nonproductive cough. There were bilateral scattered râles and rhonchi, with occasional high-pitched, musical inspiratory wheezes. Hemoglobin, red cell count and urinalysis were within normal limits. The white blood cell count was elevated to 18.6 thousand, with 60 per cent polymorphonuclear cells. Chest roentgenogram (figure 2) revealed a diffuse mottling throughout both lungs, most dense in the hilar areas and radiating well out into the periphery. This was thought to be consistent with the appearance of miliary tuberculosis. However, the diagnosis of tuberculosis was questioned, as the mildness of the constitutional symptoms and the absence of fever seemed out of keeping with such extensive pulmonary infiltration. Studies of the sputum and gastric aspirations were negative for acid-fast bacilli. The diagnostic possibilities included Boeck's sarcoid, fibrosis due to industrial inhalants, carcinomatosis, mycotic infection and acute interstitial fibrosis.

Bronchoscopy was grossly unremarkable, but cytologic examination of the bronchial aspirates was reported by Dr. George Papanicolaou as revealing conclusive evidence of a malignant neoplasm (figure 3). He did not identify the cells further. Extensive search for a possible primary neoplasm elsewhere in the body was fruitless.

The patient became progressively worse. The vital capacity on the fifteenth hospital day was only 750 c.c. (estimated normal, 2,900 c.c.), and 10 days later only 600 c.c. Subsequently, low-grade temperature elevation appeared and respirations increased to 40 to 50 a minute at bed rest. Chest roentgenograms revealed confluence of the previously described densities. On the thirty-first hospital day, a four-day course of nitrogen mustard therapy (methyl-*bis* ((β-chloroethyl)) amine hydrochloride, 1 mg./kilo.) was instituted in a vain effort to retard the rapid extension of the neoplastic process. Despite continuous oxygen administration, the patient expired on the thirty-sixth day in respiratory distress.

*Postmortem Examination:** Two hundred centimeters of serosanguineous fluid were found in each pleural cavity. The lungs weighed 1,630 gm. and were full, firm and noncrepitant. Cut surface revealed diffuse, gray-white, homogeneous tumor tissue. Tumor involvement of the bronchial tree was nowhere evident. The hilar lymph nodes were enlarged and firm and were composed of nodules of gray-white tumor tissue.

Microscopically, the findings in both cases were so similar that they may be described together. Sections from each lobe were essentially the same and revealed that the alveoli were lined by single to pseudostratified layers of nonciliated, high cuboidal to columnar cells (figures 4, 5, 6). The nuclei appeared hyperchromatic, large and vesicular. The cells were pleomorphic and some contained several nuclei. Mitotic figures could be demonstrated. Papillary projections into the alveoli were present, as was exfoliation of single or groups of tumor cells. The cytoplasm and nuclei of the desquamated cells assumed a round to oval form. Except for some thickening, the alveolar walls were for the most part unaltered. At the periphery of the lung, uninvolved alveoli were present. No involvement of the bronchial tree was noted. The tumor cells did not appear to resemble ciliated cells of bronchial

*Autopsy performed by Dr. Alexander Stevens, Jr.

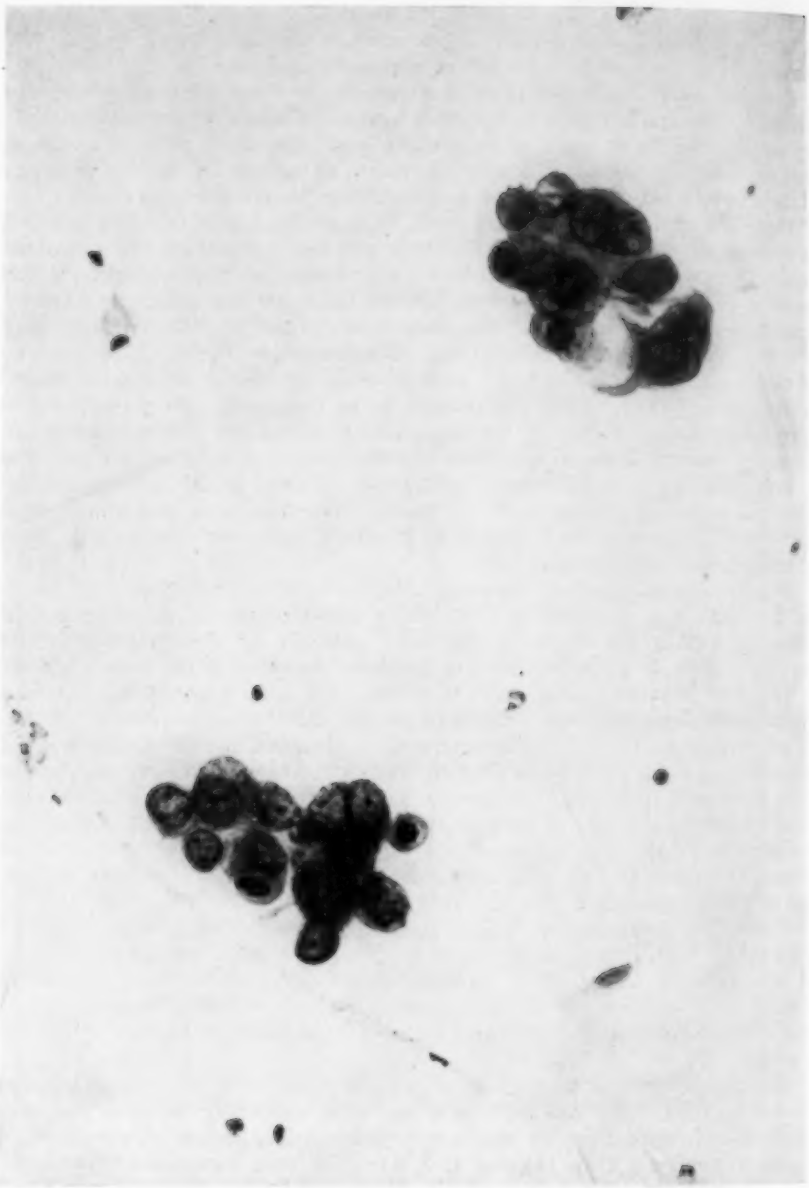

FIG. 3. *Case 2.* Smear of bronchial aspirate illustrates clusters of cells interpreted as conclusive evidence of malignancy. These appear identical to the lining cells and exfoliated cells in figure 4. (Courtesy of Dr. George Papanicolaou.) × 1200.

epithelium. Sections of the metastatic nodules in the tracheobronchial lymph nodes and liver in case 1 (figure 7) and hilar lymph nodes in case 2 (figure 8) revealed tumor similar to that found in the lung. A focal area of metastatic tumor in the vertebral marrow was also noted in the second case.

Discussion

Both cases exhibit the unique and characteristic microscopic findings of the alveolar-cell tumors. Alveoli, the walls of which appear unaltered, form the stroma, and are lined by a single to pseudostratified layer of nonciliated, high cuboidal to columnar epithelium. The formation of papillary projections and desquamation of tumor cells into the alveoli occur frequently. The desquamated cells noted in the sections of the second case (figure 4) appear identical to those in the smear of the patient's bronchial aspirations (figure 3) and are typically oval with acidophilic cytoplasm. No invasion of bronchial elements was noted on gross or microscopic examination. Although all lobes were involved, scattered sections of uninvolved alveoli could be demonstrated.

The site of origin is unexplained. There is no general agreement as to the nature or even the existence of an alveolar lining. Among those [1, 2, 3, 4, 5, 6, 7] who believe this lining is of epithelial origin, there is disagreement as to whether it is continuous. Others [8, 9, 10, 11] hold the opinion that it is mesodermal, while Ross [12] believes both epithelial and mesenchymal derivatives are present. Although different observers have studied the problem from the embryologic, histologic and pathologic viewpoints, opposite conclusions have been drawn despite the fact that many have used the same methods.

It has been suggested that these tumors are bronchiogenic in origin, arising from a single focus and metastasizing rapidly throughout the lungs.[14] Herbut [15] observed the downgrowth of bronchiolar epithelium in bronchiectasis and postulates a similar mechanism. Those [16, 17, 18] who favor a mesenchymal origin of the lining cells contend on morphologic grounds that carcinoma cannot be primary there. Neubuerger and Geever [19] leave open the question of the nature of the cells and prefer the term "alveolar-cell tumors."

In some chronic pathologic conditions, such as silicosis and tuberculosis, as well as in acute interstitial pneumonia and psittacosis, a definite alveolar lining cell has been demonstrated.[20, 21, 52] In animals, the proliferation of cells lining the pulmonary alveoli has been brought about experimentally with various irritating substances.[22, 23, 24, 25] Tumors in mice, thought to originate from alveolar lining cells, have been induced by cutaneous application and injection of aromatic hydrocarbons.[26, 27] It is of interest to note that in case 1 the patient had worked for 37 years with a mixture of tar, linseed oil, glycerin and glue, while in case 2 the patient had worked for two years with an unproved irritant, zinc oxide and rosin dust.

Although not as yet conclusive, the bulk of evidence suggests that an alveolar lining may, in response to various specific agents, proliferate and give rise to tumors.

In both cases herein reported, the alveolar lesions could not be differentiated histologically from so-called pulmonary adenomatosis, as de-

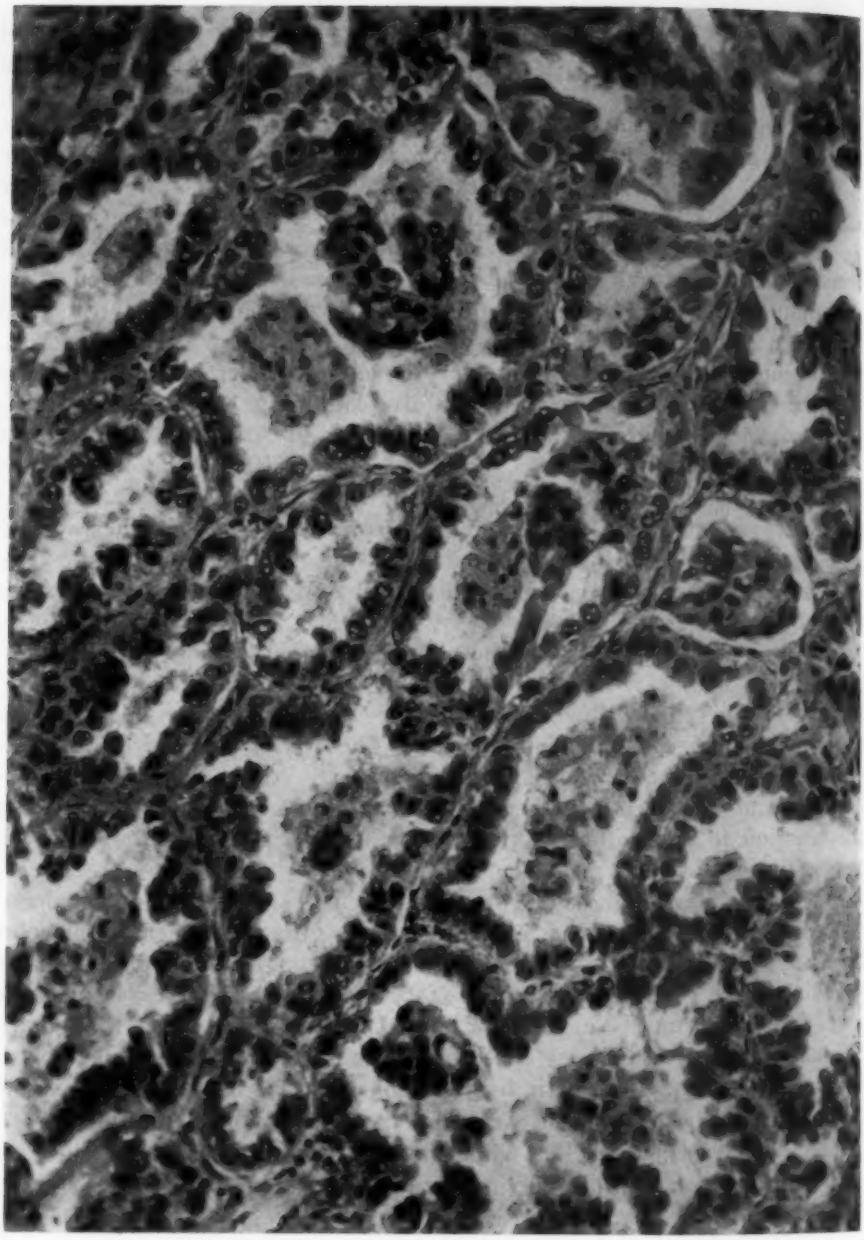

FIG. 4. *Case 11.* Section from the right lower lobe reveals tumor cells lining the alveoli with papillary projections and exfoliated cells. H. & E. × 300.

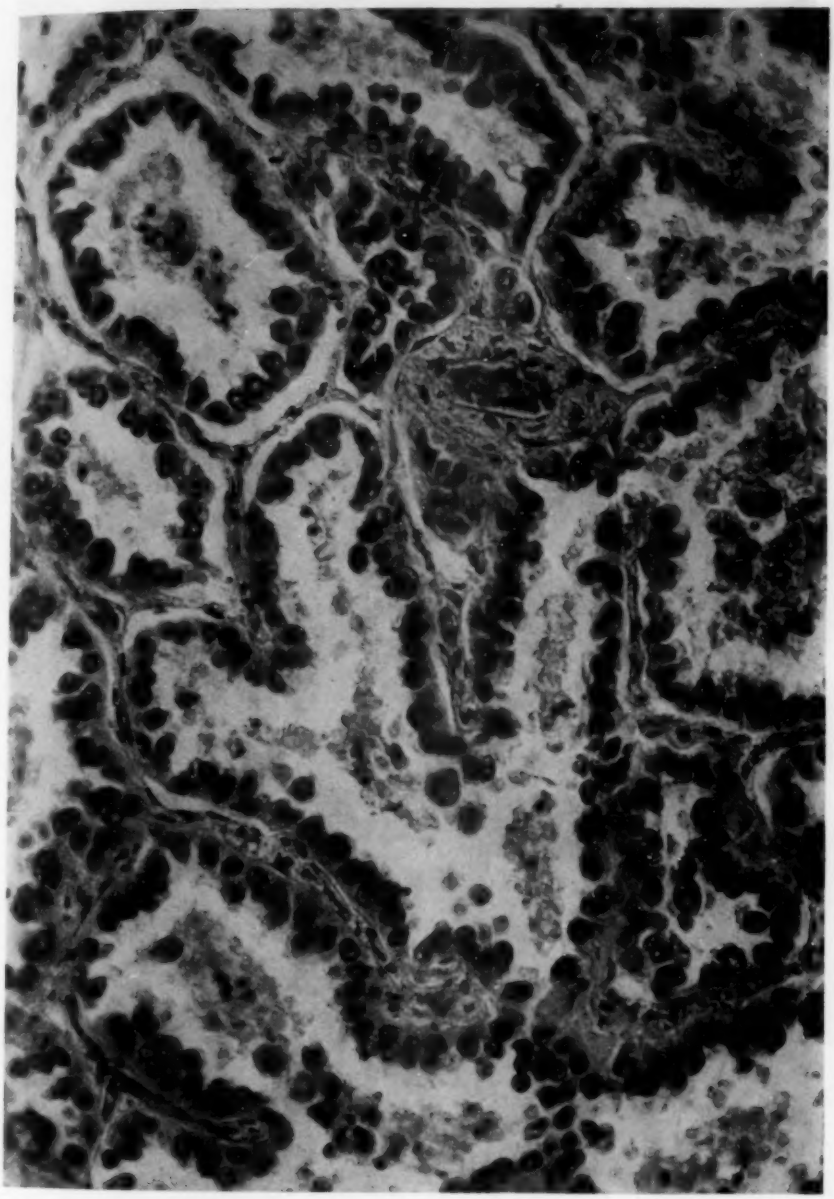

FIG. 5. *Case 1.* Section from the left upper lobe, showing the characteristic arrangement of the tumor cells. Compare with figure 4. H. & E. × 450.

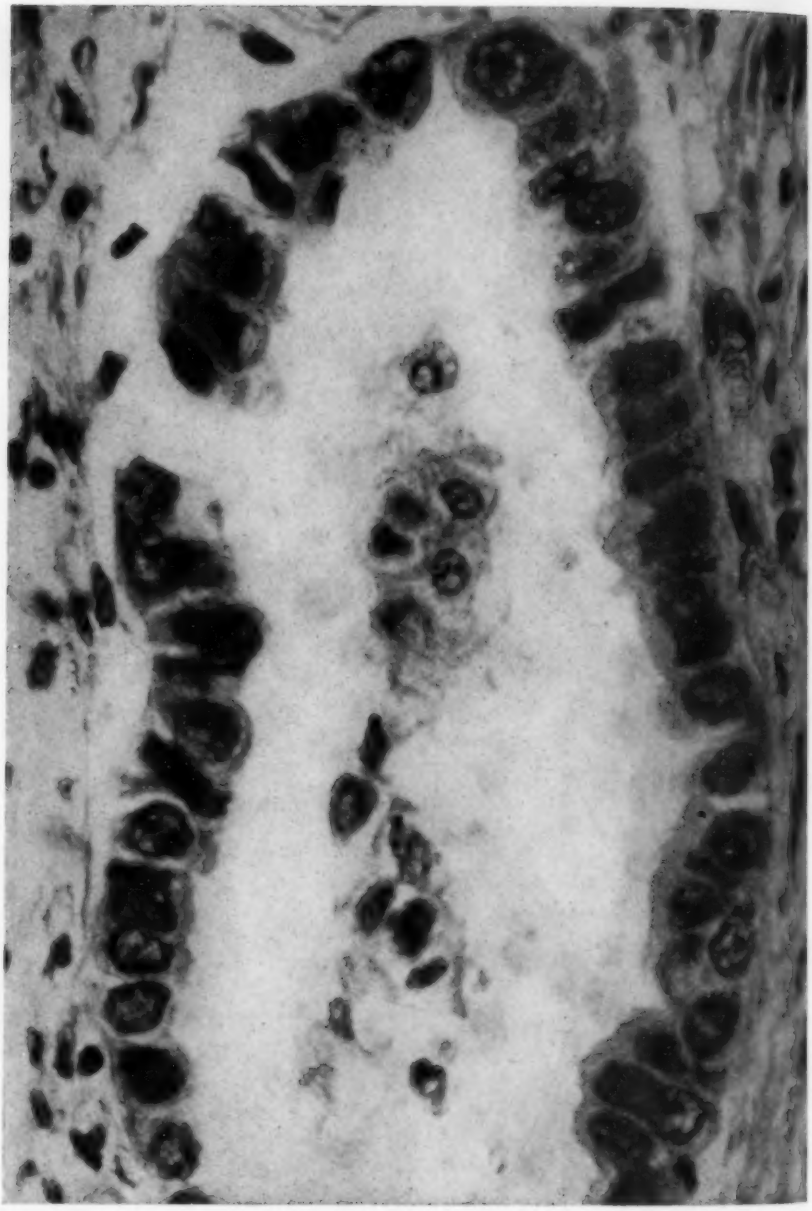

FIG. 6. *Case 1.* High power section of the right lower lobe illustrates the single to pseudostratified layers of nonciliated, high cuboidal to low columnar cells lining an alveolus. H. & E. × 1450.

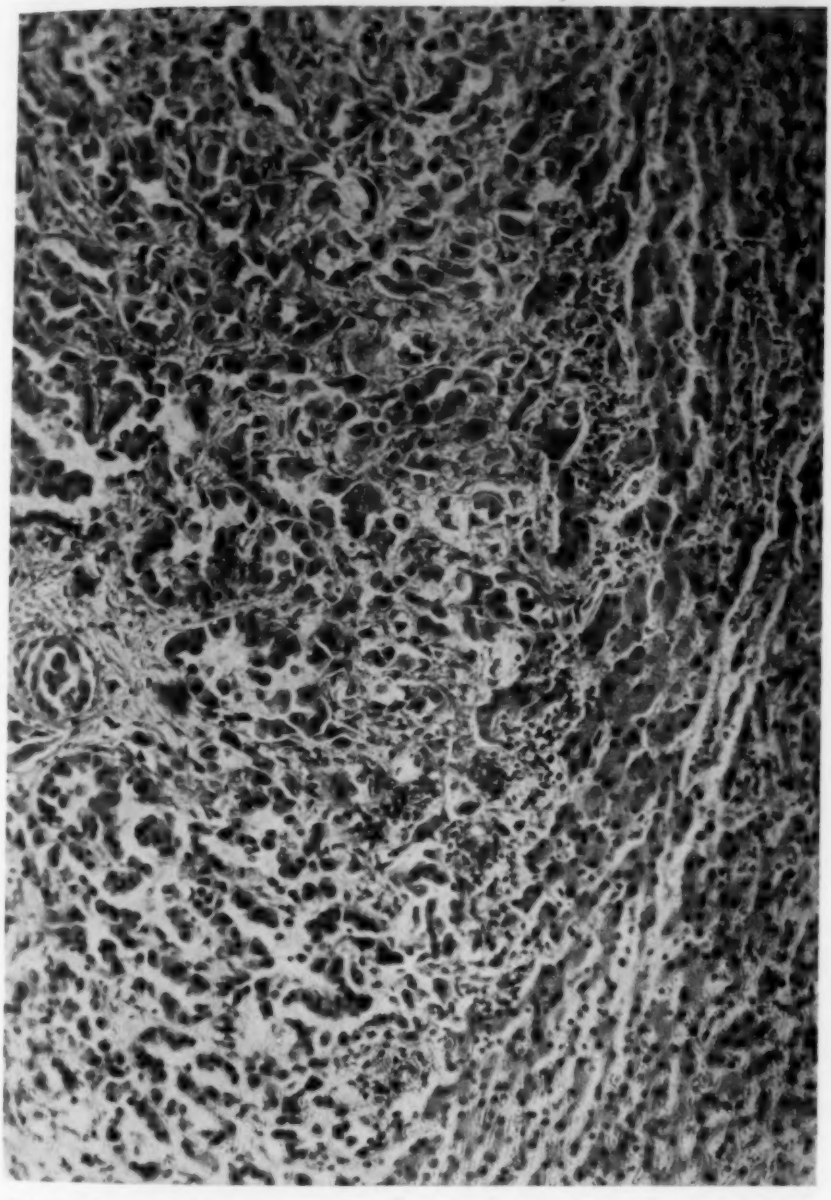

FIG. 7. *Case 1.* Metastases in the liver bear a striking cytologic and morphologic resemblance to the tumor in the lung. H. & E. × 150.

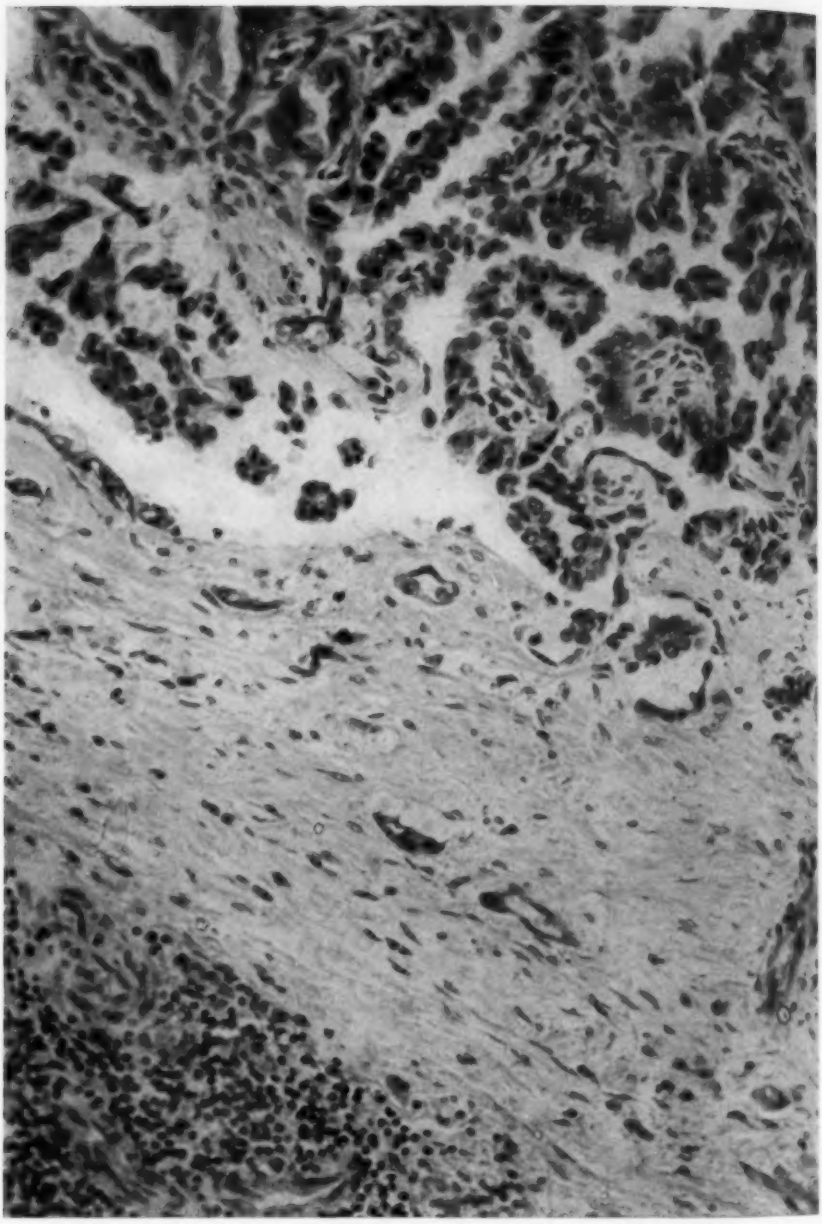

FIG. 8. *Case 2.* Section of a hilar lymph node with metastases resembling tumor in the lung. H. & E. × 150.

scribed by Briese [28] and others.[29, 30, 31, 32, 33] This resemblance has led to the suspicion that pulmonary adenomatosis is potentially malignant or precancerous.[36] Attention has also been directed to the striking morphologic resemblance of pulmonary adenomatosis in man to jaagsiekte, an endemic and infectious disease in sheep, described by Cowdry [38] and others.[39, 40] Histologically, the alveolar lesions in both species have been described as being identical.[33] In both, the alveoli are lined by a regular layer of nonciliated, high cuboidal or low columnar epithelium with papillary projections. Aynaud [41] describes a case of jaagsiekte in sheep in which metastases occurred. His findings were later confirmed by Dungal.[40] Metastases have also been demonstrated in cases included as examples of pulmonary adenomatosis.[19, 28, 42] In Bonne's case,[29] invasion of the pleura was definitely present and led him to suggest that it be called "carcinosis." "Malignant" adenomatosis has also been proposed.[43]

Thus Simon [44] notes that the criteria for malignancy are fulfilled, as metastases have been demonstrated both in jaagsiekte in sheep and pulmonary adenomatosis in man. He regards pulmonary adenomatosis as a slow-growing, eventually metastasizing tumor, and concludes that pulmonary adenomatosis and alveolar-cell carcinoma are the same. It has been suggested that the process begins as hyperplasia, stimulated perhaps by various specific agents, progressing then to pulmonary adenomatosis, and continuing on to pulmonary alveolar-cell carcinoma.[33, 45]

The infectious nature of jaagsiekte has long been recognized and has stimulated the search for an etiologic agent. Dungal [46] appears to have isolated a virus which produced similar lesions in the lungs of sheep. Recently, pulmonary adenomatosis has been described in a woman who had been in prolonged contact with sheep, of which one was proved to have succumbed to jaagsiekte.[47] Experimental injections of human lung material into laboratory animals have not reproduced the characteristic lesion.[31, 33] At present, the cause of the alveolar-cell tumor remains obscure, as is true of most neoplasms.

All investigators agree that the clinical signs, symptoms and roentgenologic findings are protean and that a conclusive diagnosis cannot be made from them.[36, 48] This condition has been variously mistaken for pulmonary tuberculosis, pneumonia, Boeck's sarcoid, pneumoconiosis, metastatic carcinoma and mycotic infection. In only one instance in the approximately 75 reported cases of alveolar-cell tumors has the antemortem diagnosis been correctly made. In this case,[33] the diagnosis was established consequent to lobectomy.

Needle biopsy and cytologic examination of the sputum are two procedures whereby the antemortem diagnosis may be established. Simon [44] presented a photomicrograph of a needle aspiration biopsy showing fairly characteristic features. In retrospect, he suggested that the diagnosis could have been made from this. Cytologic examination of the bronchial aspirates from case 2 led Dr. George Papanicolaou [49] to report the presence of con-

clusive evidence of malignancy (figure 3). His report on the sputum of Simon's case suggested malignancy. The cell type was not further identified by him in either instance. Later comparison of the slides led Dr. Papanicolaou to conclude that there were clusters of cells bearing points of similarity in both cases. However, the nuclear changes of malignancy were more pronounced in the case herein reported. As experience is gained with this tumor type and with these methods, diagnosis should be facilitated.

The second patient in this report was treated with nitrogen mustard therapy. This was considered ineffective, as it in no way altered the course of the disease.

Summary

1. Two cases are presented as examples of pulmonary "alveolar-cell carcinoma" with the clinical and pathologic findings.

2. The characteristic microscopic findings are described.

3. The controversy regarding the histogenesis of this tumor and its relationship to pulmonary adenomatosis in man and to jaagsiekte in sheep is briefly discussed.

4. Pulmonary needle aspiration biopsy and cytologic examination of sputum or bronchial washings are suggested as measures aiding in the diagnosis.

Addendum

Since this article was submitted, a patient with a similar neoplasm has been studied. Treatment with nitrogen mustards was without benefit. The diagnosis of "alveolar-cell" carcinoma was suggested by Dr. Papanicolaou following examination of sputum and bronchial washings. This was confirmed at autopsy, where the gross and microscopic findings were similar to those described above. Metastases were found in the regional lymph nodes, heart and adrenals.

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ERYTHEMA NODOSUM: THE POSSIBLE SIGNIFICANCE OF ASSOCIATED PULMONARY HILAR ADENOPATHY *

By C. Clifford Johnson, M.D., Norbert O. Hanson, M.D., and C. Allen Good, M.D., *Rochester, Minnesota*

Erythema nodosum has been described by Spink [1] as "a nonspecific inflammatory reaction of the skin to a variety of bacterial, toxic and chemical agents." It is characterized, according to Spink, as an acute febrile illness with painful, nodular, erythematous lesions on shins and forearms and by joint pains and malaise. Hilar adenopathy is associated with the above signs in some cases but has not been recognized generally as an accompaniment of the condition. Three cases of erythema nodosum in which hilar adenopathy was a feature were encountered at the Mayo Clinic in a period of four months, and in each instance both the cutaneous lesions and the thoracic findings disappeared while the patient was under observation. Consequently, it was thought worth while to investigate, among patients at the institution named, the frequency of occurrence of hilar adenopathy in association with the condition. Before we report the results of this investigation, however, brief reference will be made to some of the work of others as that work relates to erythema nodosum with associated pulmonary hilar adenopathy and to associated diseases which might be of causal significance.

Previous Studies

Erythema nodosum has been considered a disease sui generis by some,[2] but by others as a manifestation of diseases such as tuberculosis,[3, 4, 5, 6] sarcoidosis,[7] rheumatic fever [8] and coccidioidomycosis.[9, 10, 11, 12, 13] It also has been encountered in association with miscellaneous conditions, including lymphogranuloma inguinale,[14] leprosy,[7] other infections,[1, 7, 15] and as an accompaniment of sensitivity to a variety of drugs, such as bromides, iodides and sulfonamides.[16] Studies from different localities indicate that etiologic factors may differ to a large extent according to geographic location.

Tuberculosis. In the Scandinavian countries, erythema nodosum among children has been considered a manifestation of tuberculosis in 95 per cent of cases, according to Wallgren,[4, 5, 6] who has expressed the belief that erythema nodosum is a manifestation of allergy to tuberculosis. Recently two extensive studies of erythema nodosum among adults in Sweden have been made independently by Skiöld [17] and Löfgren.[18] Skiöld found that about half of his series of 354 cases of erythema nodosum were of tuberculous

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origin. Löfgren found tuberculosis to be the significant causal agent in 104 (58.4 per cent) of the 178 cases which he personally observed. Of the 178 cases, in 78 (43.8 per cent) the presence of tuberculosis of recent type was verified.

"The association of tuberculosis and erythema nodosum is most common in children and rare in adults," wrote Spink [1] in reporting his study of the etiology of erythema nodosum. He found enlarged hilar nodes in three of 48 cases in which roentgenograms of the thorax were available to him. Of the remaining 45, roentgenologic findings were negative in 30; in two there was evidence of old tuberculosis of the lung with calcification; in one an abscess of the right upper lobe was found, and in one slight clouding in the region of the left apex was apparent. In the remaining 11 of the 45 cases, the variable findings were of no apparent significance. Of 133 cases of erythema nodosum, Spink found evidence of active tuberculosis in only one case.

Tuberculosis and erythema nodosum may seem more closely related when the hilar adenopathy which has just been mentioned is also present. Löfgren [18] found pulmonary lesions of "fresh" appearance in 140 (78.7 per cent) of the 178 cases of erythema nodosum which he studied. Of these 140, in 102 (57.3 per cent of 178) unilateral hilar enlargement was detected by roentgenographic examination. In 77 of the 102 cases, parenchymal infiltration was present in association with the unilateral hilar enlargement, while in 25 cases, parenchymal infiltration was absent. Bilateral hilar glandular enlargement was found in 30 cases of the 140 (16.8 per cent of 178). In 20 of the 30 there was an associated parenchymal infiltration and in 10 there was none. In the remaining eight of the 140 cases there were parenchymal lesions, apparently of recent origin, but no recognizable hilar enlargement. Of the cases in which Löfgren believed that tuberculosis was the etiologic agent of the erythema nodosum, unilateral hilar adenopathy was present in 86 per cent, while bilateral hilar adenopathy was present in only 9 per cent.

A study of tuberculous hilar and mediastinal adenopathy was made by Widmann, Ostrum and Fetter.[19] Hyperplastic tuberculosis, they stated, is usually a childhood disease but may affect adults as a primary infection, and evidence of it may be seen on roentgenograms as an enlargement of the hilar shadow. Such a shadow may be present for years, while the patient remains free of symptoms. In reporting a study of 65 such cases, however, the investigators just named did not once mention that erythema nodosum was an associated finding.

Paul and Pohle [20] studied 42 patients admitted to the Wisconsin General Hospital with a diagnosis of erythema nodosum. All except one of these were adults, and thoracic roentgenograms of 20 of them had been made. In nine of the 20 cases hilar adenopathy was the sole finding derivable from roentgenograms of the thorax. In three cases of the nine the hilar adeno-

pathy was slight, and in six, moderate to marked. In two of the nine cases hyperplastic tuberculosis was proved to be present, and in four of the remaining seven tuberculosis was considered to be present but proof never was obtained. Paul and Pohle stated that all patients with erythema nodosum should have the benefit of roentgenograms of the thorax, in view of the possibility that tuberculosis is present.

It has been observed by Symes [21] that acute, fatal tuberculosis is peculiarly likely to develop within six months of the diagnosis of erythema nodosum. Tuberculous meningitis is not an unknown accompaniment of erythema nodosum.[21]

Gray,[3] in Britain, reported nine cases of erythema nodosum in which there was a history of the patients' having been in contact with persons who had tuberculosis. In all cases Mantoux tests were positive. Gray expressed the belief that in all cases of erythema nodosum the etiologic factor should be considered to be tuberculosis until proved otherwise. Moreover, Gamstedt [22] has observed that a high percentage of patients will exhibit a negative tuberculin reaction prior to development of erythema nodosum but that a positive one will develop at the time of the appearance of the cutaneous lesions or shortly thereafter.

Sarcoidosis. Kerley [7] expressed the belief that there may be a relationship between erythema nodosum and sarcoidosis. Of 12 cases of erythema nodosum with hilar adenopathy which he reported, iridocyclitis developed in one and corneal ulceration with iritis in another. The same author, in commenting on the significance of radiologic manifestations of erythema nodosum, stated that part of this symptom complex may consist of massive enlargement of the bronchial and hilar nodes and also diffuse infiltration of the lungs. These features, he further stated, may be asymptomatic and indistinguishable from manifestations of sarcoid. He reported 12 cases; in 10 of them the hilar enlargement was bilateral.

In a study of 142 thoracic roentgenograms suggestive of sarcoidosis, King [23] found that only 111 of the corresponding cases were proved instances of Boeck's sarcoid. Of the 142 cases, seven were instances of erythema nodosum in which the roentgenologic appearance was "exactly like that of sarcoid." King wrote further: "Erythema nodosum gives a chest roentgenogram indistinguishable from that of sarcoid disease."

Rheumatic Fever. Mackenzie [8] considered erythema nodosum and rheumatic fever to be related diseases. He made a diagnosis of rheumatic fever in 19 per cent of 233 cases of erythema nodosum. Results of this study have not been accepted by many readers, however. G. See,[24] in 1859, stated that the joint pains of erythema nodosum differ from those of rheumatic fever; in the former, he wrote, swelling and redness of joints are absent and the joints are capable of motion.

Trousseau [25] and Barlow [26] each stated that he never had heard a cardiac murmur in a case of erythema nodosum, and Harrison [27] pointed out that

erythema nodosum seldom recurs, whereas rheumatic fever frequently does recur. Erythema nodosum, however, has a seasonal incidence, may occur in epidemics [2, 5] and, in Löfgren's study, recurrences were found in 10 per cent of the 178 cases studied.

Poppel and Melamed,[28] in their study of 88 cases of erythema nodosum, found evidence of rheumatic fever in seven and of infection of the upper part of the respiratory tract in 49; in the remaining 32 cases various conditions were associated with the erythema nodosum.

In 1937, Keil [29] differentiated erythema nodosum from rheumatic fever, stating that exaggerated hilar roentgenologic shadows had been estimated to be present in from 50 to 90 per cent of cases of erythema nodosum among children. This author reported that he had seen this sign also in roentgenologic examination of adults with erythema nodosum.

Coccidioidomycosis and Other Mycotic Infections. Dickson,[9, 10] in 1937 in California, noted that a large number of people in the San Joaquin Valley had erythema nodosum and that, from the sputum of five of them, *Coccidioides immitis* was cultured. The onset of coccidioidomycosis was acute, with moderate fever, malaise, joint pains and bronchitis. Eight to 15 days later erythema nodosum, frequently accompanied by parenchymal and hilar pulmonary involvement, was apparent. As the result of an inquiry among physicians in the San Joaquin Valley, Dickson [11] in 1938 was able to report occurrence of 354 cases of this form of erythema nodosum in that locality during a period of 16 months. The roentgenologic appearances in the disease were described by Dickson and Gifford [12] as follows: "The typical picture includes evidences of enlargement of the hilar glands, branching shadows from the hilar regions of the lungs and more or less scattered areas of shadows indicating involvement of the parenchyma of the lung, either in the upper or the lower lobes. Signs of pleurisy, pleurisy with effusion or interlobar empyema may be seen at times." In a majority of cases the roentgenologic thoracic changes are transient and disappear within several weeks or months; in a minority of cases the disease progresses and a chronic inflammatory granulomatous process results.

Smith,[13] in 1940, stated that erythema nodosum developed in about 5 per cent of a series of cases of coccidioidomycosis. In all of the series the skin test was positive for coccidioidomycosis. Carter [30] reported a series of thoracic roentgenograms of patients with mycotic infections. In a large percentage of these, mediastinal or hilar adenopathy was evident.

Miscellaneous Conditions. In Spink's [1] study of erythema nodosum, a streptococcal infection was found in some organ of the body in a large majority of cases. Löfgren,[18] in his detailed investigation in Sweden, found streptococcal infection to be second only to tuberculosis as an etiologic factor of erythema nodosum. Streptococcal infection was considered to be the significant causal factor in 30 (16.9 per cent) of the 178 cases personally observed by him. Bargen [31] found erythema nodosum as a complication

in a small percentage of cases of chronic ulcerative colitis. Poppel and Melamed [28] found six of 88 cases of erythema nodosum associated with chronic ulcerative colitis. Löfgren [18] found 44 of 178 cases of erythema nodosum which he felt were not of tuberculous or streptococcal origin. In 17 of the 44, hilar adenopathy was found, and with reference to nine of the 17 cases Löfgren employed the term "benign lymphoma" because no cause for the erythema nodosum could be found.

Many of the observers who have been named in the foregoing paragraphs mentioned enlargement of the pulmonary hilar lymph nodes. In this respect three other articles should be cited. Sosman, Bailey and Armstrong [15] stated that they found enlarged hilar nodes in eight of 41 cases of erythema nodosum. They further stated that these lesions did not undergo calcification or ulceration; they did not form cavities or leave fibrosis on healing. Poppel and Melamed,[28] in their review of erythema nodosum mentioned in a previous paragraph, found roentgenograms relative to 56 of the 88 cases. In 12 of the 56 cases hilar lymph nodes were enlarged, and in three they gave evidence of calcification. The investigators named expressed the opinion that hilar adenopathy and erythema nodosum are related. Bonnet [32] reported a case in which a soldier presented bilateral hilar adenopathy and erythema nodosum. The thoracic changes disappeared approximately four months after diagnosis had been made.

Present Study in General

Beginning with April, 1948, records of the Mayo Clinic were reviewed in reverse chronologic order until records of 100 cases had been obtained in which the dermatologic diagnosis of erythema nodosum was unequivocal and in which, also, roentgenograms had been taken while cutaneous lesions had been present. These records were examined with respect to sex and age of patients, duration of symptoms, sedimentation rate, relationship to hilar adenopathy, symptoms usually associated with erythema nodosum, and possible causative agents.

There were 77 females and 23 males. Their ages by decades are recorded in table 1. Ages ranged from 10 to 73 years. The fact that only three patients were 10 years of age, and that only two others were less than

Table 1

Distribution of Patients by Decades of Life

Decade	Patients
10–20	8
21–30	14
31–40	23
41–50	28
51–60	19
61–70	7
71–80	1
Total	100

TABLE II

Duration of Symptoms

Duration	Cases
1–2 weeks	75
4–8 weeks	6
6–12 months	4
2 years (recurrent)	2
4 years (recurrent)	1
6 years (recurrent)	6
10 years (recurrent)	3
15 years (recurrent)	1
20 years (recurrent)	2
Total	100

19 years of age, makes this largely a study of adults. Duration of symptoms (table 2) varied from two weeks to 20 years. In 97 cases the sedimentation rate was determined by the Westergren method. In 84 per cent the rate was elevated, and in 32 per cent it was more than 100 mm. per hour by the Westergren method (table 3).

The incidence of diseases associated with erythema nodosum, and possibly causative of it, is listed in table 4. Relevant textual comment on the series of 100 cases will follow as closely as possible the order of the comment on previous studies.

Tuberculosis. Of 11 patients who were subjected to a tuberculin test, two gave a positive reaction and the remaining nine a negative reaction. Sputum and gastric washings of two additional patients were negative for tubercle bacilli. One other patient had a tuberculous cavity and another died from tuberculous meningitis six months after onset of erythema nodosum. None of the patients mentioned in this paragraph had hilar adenopathy.

Sarcoidosis. As noted (table 4), three patients had uveitis, iritis and chorioretinitis, but there was no other evidence to support a diagnosis of sarcoidosis.

Coccidioidomycosis. One patient had erythema nodosum and coccidioidomycosis. Shortly before examination this patient had visited Arizona.

TABLE III

Sedimentation Rate (Westergren)

Sed. Rate, mm. per hr.	Cases
0–20	16
21–30	12
31–40	5
41–50	8
51–60	9
61–70	5
71–80	4
81–90	4
91–100	3
101–110	12
111–120	19
Total	97

Skin tests for evidence of coccidioidomycosis were strongly positive. Roentgenograms revealed parenchymal pulmonary infiltration of the left hilar region. This infiltration was considered, in our study, to be a specific manifestation of coccidioidomycosis, and this case is not included among the nine in which hilar adenopathy was present in association with erythema nodosum.

Miscellaneous Conditions. In 26 cases, infection of the upper part of the respiratory tract preceded the appearance of erythema nodosum. In two of these, streptococci had been cultured from the throat. Several of the 26 patients were thought to have rheumatic fever on admission but further observation ruled out this diagnosis. Chronic ulcerative colitis, dental infection, appendicitis, cholecystitis, bronchiectasis and meningococcemia were some of the other infections which were found associated with erythema nodosum. Of the series of cases investigated, in 15 erythema nodosum was

TABLE IV

Diseases Associated with Erythema Nodosum

Associated Disease	Cases
None	30
Unspecified infection of upper respiratory tract	26
Dental infection	4
Some other infections (appendicitis, cervicitis, cholecystitis)	8
Tuberculosis (clinical or pos. tuberculin test)	4
Chronic ulcerative colitis	4
Coccidioidomycosis	1
Uveitis, iritis, chorioretinitis	3
Bronchiectasis	1
Meningococcemia	1
Sensitivity to sulfonamides	8
Sensitivity to bromides (above 85 mg. per 100 c.c. of blood)	7
Carcinoma or sarcoma	3
Total	100

considered to be attributable to sensitivity to drugs, in seven to bromides and in eight to sulfonamides. In one additional case, not identified in table 4, thiouracil and iodine may have been causative factors in the erythema nodosum. In none of the cases in which sensitivity to drugs was noted was there hilar enlargement.

THE NINE CASES OF THE PRESENT STUDY IN WHICH PULMONARY ADENOPATHY WAS FOUND

Roentgenologic examination of the thorax in the series of cases under consideration revealed hilar adenopathy in nine; eight in which the adenopathy was bilateral, and one in which it was unilateral. The nine patients were between 38 and 61 years of age (table 5); of these, seven were women and two were men. In five of the nine cases follow-up films were available, and in four of these five the hilar enlargement had disappeared. In three of the four the hilar adenopathy cleared in a period of one to seven months

TABLE V

Summary of the Nine Cases of Erythema Nodosum in Which Pulmonary Hilar Adenopathy Was Found

Case	Age; Sex	Complaints	Duration	Associated Diseases	Sed. Rate WBC	Negative Tests	Body Fluids	Thoracic Roentgenograms
1	38 F	Fever (99°–102° F.) Malaise Joint pains Aching Fatigue Chills Nausea Diarrhea Nodules, legs	3 weeks	Carcinoma Breast removed 14 yrs. before "Flu"	45 7,700	Tuberculosis	Blood cult., neg. Serum prot. 6.5 Serum alb. 4.2 Serum glob. 2.2	Apr. 7, 1948: Bilateral hilar adenopathy Aug. 31, 1948: Negative
2	61 M	Fever (101°–104° F.) Malaise Joint pains Aching Chills Headache Nodules, legs Cough	2 weeks	Epilepsy "Flu"	112 6,900	Brucellosis Typhoid Paratyphoid Coccidioidomycosis Tuberculosis	Blood cult., finally neg. Spinal fluid neg. Serum prot. 6.5 Serum alb. 3.8 Serum glob. 2.7	Feb. 26, 1948: Moderate bilateral hilar adenopathy (sarcoid, lymphosarcoma?) Sept. 22, 1948: Negative Bones of hands, negative
3	42 F	Fever (100° F.) Ankle pain and edema Aching Nodules, legs	2 months	Diabetes	47			Jan. 2, 1947: Bilateral hilar adenopathy Sept. 5, 1948: Negative

TABLE V—*Continued*

Case	Age; Sex	Complaints	Duration	Associated Diseases	Sed. Rate WBC	Negative Tests	Body Fluids	Thoracic Roentgenograms
4	50 F	Fever Joint pains Ankle edema Nodules, legs Cough	1 month	Emotional shock	76 5,100	Brucellosis	Blood smear, neg. Blood cult., neg. Serum prot. 7.1 A.G. ratio, 1.81 Serum calcium 10.3 Serum uric acid 4.5	Feb. 7, 1946: Increased bilateral hilar markings Mar. 9, 1946: Negative Bones of knees, pelvis, ankles, negative
5	48 F	Fever (103° F.) Joint pains Nodules, arms, legs	1 month	Suppurative antral-oral fistula	64 10,600		Blood cult., neg.	Sept. 4, 1945: Bilateral hilar adenopathy No follow-up roentgenograms
6	60 F	Fever (100° F.) Ankle edema Nodules, legs	3+ months	None	118 6,400		Blood cult., neg.	July 30, 1945: Enlarged hilar nodes, right No follow-up roentgenograms
7	56 M	Fever (100° F.) Joint pains, stiffness Swelling, legs and ankles	3+ months	Sore throat "Cold"	66 9.900	Brucellosis Paratyphoid Typhoid Coccidioidomycosis Blastomycosis Tuberculosis	Serum prot. 6.1 Serum alb. 3.2 Serum glob. 2.9	Apr. 12, 1948: Enlarged hilar nodes, bilateral Sept. 22, 1948: Hilar markings still present Bones of hands and feet, negative
8	52 F	Fever (100° F.) Aching Conjunctivitis Tubotympanitis Nodules, legs	1 month	"Flu"	110 11,200		Blood cult., neg.	June 2, 1945: Enlargement both hilar shadows No follow-up roentgenograms
9	46 F	Fever (100° F.) Malaise Aching Nodules, legs	1 month	None	58 8,500			May 28, 1947: prominence of both hilar shadows No follow-up roentgenograms

from the time of the initial examination, and in the fourth case the thoracic film was negative 20 months after the initial examination. The one patient whose hilar changes persisted seven months after the initial examination also had persisting cutaneous lesions of erythema nodosum. With respect to preceding and associated diseases, four of the nine patients had symptoms of an infection of the upper part of the respiratory tract prior to the appearance of erythema nodosum. One had diabetes, one had an alveolar antral fistula, and three had no other disease prior to the onset of the erythema nodosum, although one of the three had sustained an emotional shock.

Cases 1 and 2 of table 5 will be reported in some detail because of their pertinence with regard to differential diagnosis.

Case 1. A white woman, 38 years of age, was asked to report to her physician because of unusual findings in thoracic roentgenograms made in the course of a county chest survey.

In 1934 she had undergone radical left mastectomy because of adenocarcinoma, grade 2. There had been no evidence of recurrence. She had had a "flulike" illness, accompanied by diarrhea, nausea and vomiting, 10 days prior to her registration. Three days later the following symptoms and signs had developed: migratory pains of the joints; erythematous, painful, subcutaneous nodules on both legs; a temperature ranging from 99° to 102° F., and marked malaise.

On examination at the Mayo Clinic April 8, 1948, the woman appeared ill. Her temperature was 99° F. and the pulse rate was 86 per minute. Blood pressures were 120 mm. of mercury systolic and 76 mm. diastolic. Except for the surgical scar in the region of the left breast, abnormal physical signs were limited to the lower extremities; on the legs were found several large, tender, indurated, subcutaneous nodules characteristic of erythema nodosum, and pitting edema, grade 1, of the ankles.

Laboratory studies gave some significant results. The concentration of hemoglobin was 11.1 gm. per 100 c.c. of blood. Erythrocytes numbered 3,500,000 and leukocytes 7,700 per cu. mm. of blood; the differential count was normal. The sedimentation rate of erythrocytes was 45 mm. in one hour by the Westergren method. Nothing abnormal was found by determination of the albumin-globulin ratio or of the concentration of serum protein. Urinalysis disclosed no remarkable findings. Blood culture, electrocardiograms and tuberculin testing with a purified protein derivative of tuberculin all gave negative results. A roentgenogram disclosed bilateral hilar adenopathy and a calcified Ghon complex in the middle of the right pulmonary field. In view of the previous history of carcinoma of the breast, the adenopathy was thought at first possibly to represent metastasis.

The patient was hospitalized and salicylates were administered. In a week's time, most of her symptoms had disappeared. Subsequent to her dismissal from hospital, roentgenograms made on August 31, five months from the onset of symptoms, disclosed no evidence of hilar adenopathy. The calcified Ghon complex in the middle of the right pulmonary field remained (figures 1*a* and *b*).

Case 2. A white man, 61 years of age, registered at the clinic February 21, 1948, complaining of malaise, painful joints, generalized aching, chills, cough, fever and retroörbital headache of three weeks' duration.

In the past, epileptiform convulsive seizures occurring over a period of four years had been controlled by administration of dilantin sodium. Two weeks before the patient's admission, painful, hard, red, subcutaneous nodules had developed on the lower parts of both legs. His temperature had varied between 102° and 104° F.

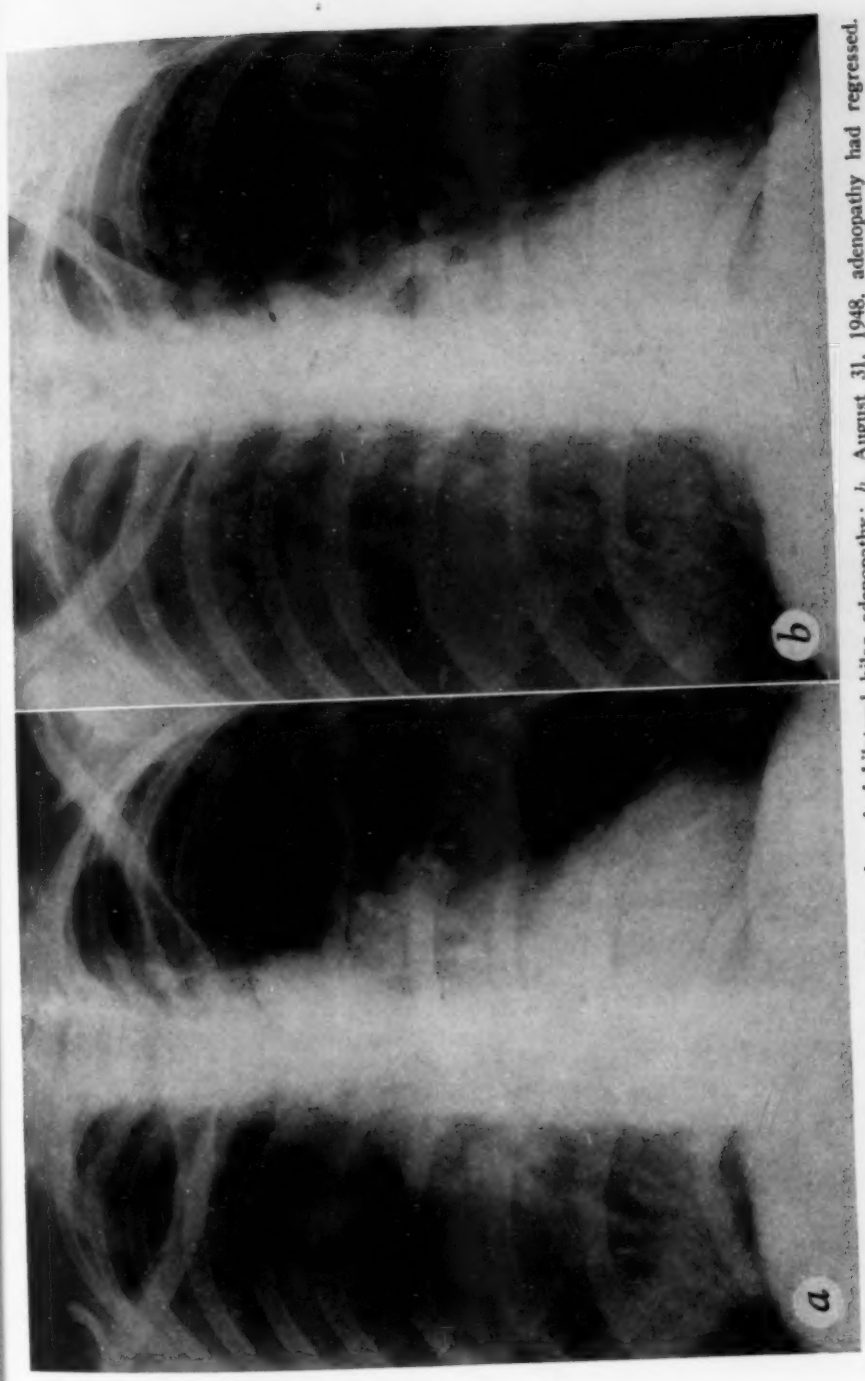

FIG. 1. (*Case 1*) *a*. April 7, 1948, evidence of marked bilateral hilar adenopathy; *b*. August 31, 1948, adenopathy had regressed.

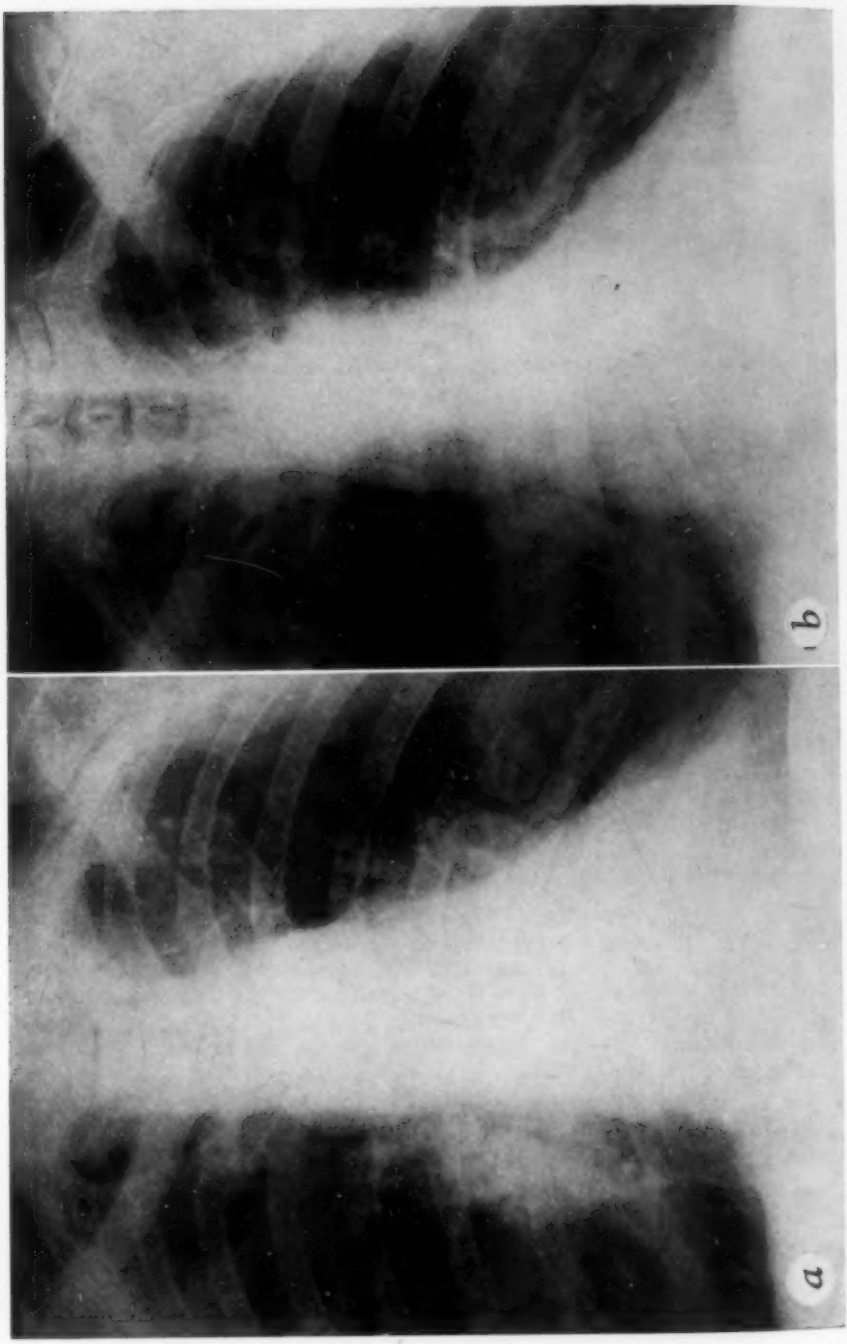

FIG. 2. (*Case 2*) *a*. February 26, 1948, evidence of bilateral hilar and right mediastinal adenopathy; *b*. September 22, 1948, adenopathy had almost disappeared.

The man was well developed and, at the time of his examination, his temperature was 101° F., his pulse rate was 90 per minute, and his blood pressure was 130 mm. of mercury systolic and 64 diastolic. Abnormalities were not found in the ears, eyes, nose, throat, thorax or abdomen. On the anterior surfaces of both legs were many tender, hard, red, indurated subcutaneous nodules.

Even though some of the laboratory studies gave negative results, they were worth while in so puzzling a case. The concentration of hemoglobin was 13.3 gm. per 100 c.c. of blood, erythrocytes numbered 4,300,000 and leukocytes 6,800 per cu. mm. of blood. The sedimentation rate of erythrocytes was 107 mm. in one hour by the Westergren method. The values for total serum protein and the albumin-globulin ratio were essentially within normal limits. One blood culture was positive for *Aerobacter aerogenes*, but in five subsequent blood cultures neither this microörganism nor others were found. Because of the initial positive culture for *Aerobacter aerogenes*, streptomycin was administered for a period of seven days. Results of agglutination tests for brucellosis, typhoid fever and paratyphoid fever were negative, as was a skin test for coccidioidomycosis. A skin test for tuberculosis, using 0.0002 mg. of purified protein derivative of tuberculin, gave a negative result, but when using 0.005 mg. a 1 plus reaction resulted. A cephalin-cholesterol flocculation test gave no evidence of abnormal hepatic function. Urinalysis disclosed no remarkable findings. Roentgenograms of the thorax were interpreted as giving evidence of hilar adenopathy; lymphoblastoma and sarcoidosis were suggested as possible etiologic causes. Roentgenograms of the bones of the hands did not display characteristics suggestive of sarcoidosis.

Under treatment with salicylates and streptomycin, the patient's condition gradually improved. In a thoracic roentgenogram made September 22, 1948, seven months from the date of the patient's admission, evidence of abnormality was not found (figures 2*a* and *b*).

Comment

Case 1 demonstrates the difficulties that can be encountered when a patient presents himself with hilar adenopathy and gives a past history of carcinoma. The fact that, as a rule, malignancy would not be expected to spread to hilar nodes bilaterally, in the absence of other evidence of recurrence, justified doubt that the hilar adenopathy was due to metastasis. The presence of erythema nodosum, and the fact that the hilar adenopathy gradually disappeared after disappearance of evidences of erythema nodosum, led to the tentative belief that the two were associated from the standpoint of etiology. The patient in recent years had not lived or traveled in areas where coccidioidomycosis is known to be prevalent. This patient did have a Ghon complex but there was no evidence of activity relative to it and, since the skin test was negative, there seemed no reason to suspect tuberculosis as a cause of the hilar enlargement. Skin tests for evidence of histoplasmosis were not made.

In case 2, the massive character of the hilar enlargement might lead the observer to consider sarcoidosis or lymphosarcoma as the cause of the enlargement. However, the normal value for serum protein, the absence of changes in bones of the hands, the absence of cutaneous lesions such as are seen in sarcoidosis, and the absence of uveoparotid involvement made the diagnosis of sarcoidosis improbable. There was no other evidence to support a diagnosis of lymphosarcoma. With the vanishing of hilar adeno-

FIG. 2. (*Case 2*) *a*. February 26, 1948, evidence of bilateral hilar and right mediastinal adenopathy; *b*. September 22, 1948, adenopathy had almost disappeared.

pathy after the symptoms of erythema nodosum had resolved, this case seemed to represent another instance in which the hilar adenopathy might be a manifestation of erythema nodosum of nonspecific etiology. The weakly positive tuberculin skin reaction was considered of doubtful significance. Sensitivity to dilantin sodium as an etiologic factor of the erythema nodosum in this case seems improbable, because administration of the substance was continued during the period of observation as well as subsequent to regression of the cutaneous lesions and the hilar adenopathy.

In case 4 (table 5) the hilar enlargement disappeared within one month of the subsidence of erythema nodosum. In case 3, the patient returned to the clinic 20 months after her admission and, on her re-admission, evidence of hilar enlargement was absent. In this case we do not know exactly how long it took for the hilar enlargement to vanish. In case 7, hilar nodes were still enlarged five months after their enlargement first had been noted, but evidence of the erythema nodosum persisted and, if our conjecture is correct that hilar enlargement and erythema nodosum are associated, we could not expect the adenopathy to have disappeared. In this case skin tests for tuberculosis, coccidioidomycosis and blastomycosis gave negative results and the values for serum protein were within normal range. In cases 5, 6, 8 and 9, follow-up roentgenograms were not available, but there seems to have been no cause for the hilar enlargement unless erythema nodosum constitutes such a cause. In case 6 of these four cases, the hilar adenopathy was unilateral. These nine patients were adults and there seems no reason to believe that tuberculosis was responsible for the hilar enlargement.

Partial Summary and Tentative Conclusions

In the records of the nine cases in which pulmonary hilar adenopathy was present, no disease process other than erythema nodosum could be found which might be the cause of the hilar enlargement. The fact that, in four of the five cases in which follow-up study was possible, hilar enlargement disappeared following recession of the erythema nodosum, fortifies our tentative belief that hilar enlargement may be an associated manifestation of erythema nodosum of nonspecific etiology.

We feel that if evidence of hilar adenopathy is found on roentgenologic examination of the thorax in a case of erythema nodosum, the thought should be entertained, along with consideration of other possibilities (notably tuberculosis, coccidioidomycosis and sarcoidosis), that the hilar enlargement may be simply a part of erythema nodosum of nonspecific etiology. Disappearance of the hilar enlargement probably may be anticipated as the erythema nodosum subsides.

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THE ELECTROCARDIOGRAPHIC CLUE TO VENTRICULAR ANEURYSM *

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EXAMINATION of the postmortem records of 99 patients with myocardial infarction who died during the last three years at the Peter Bent Brigham Hospital showed nine instances (or 9.9 per cent) with aneurysm of the ventricle. This is defined as a marked thinning of the ventricular wall observed fluoroscopically to bulge outward with inward systolic contraction of the remainder of the ventricle, or judged from its postmortem appearance to be large and thin enough to be likely to bulge outward in this manner during ventricular systole. This incidence corresponds quite closely to the general experience of pathologists.[1] Since many aneurysms are diagnosed by the pathologist merely as old myocardial infarcts, it seems reasonable that this frequency of 10 per cent may be regarded as a minimum. About 100,000 persons die in the United States each year with myocardial infarction.[2] If the frequency of 10 per cent noted above is representative of the true incidence, there should be 10,000 persons in this country who develop ventricular aneurysms every year. Yet only an insignificant proportion of those found at autopsy are diagnosed ante mortem With the exception of rupture of a ventricular aneurysm, which is very rare, the diagnosis of ventricular aneurysm carries no therapeutic or prognostic implication distinct from the entire group, and its recognition is a matter of very little practical moment. By and large, there is no evidence that the outlook of patients with ventricular aneurysm differs essentially from that of the entire group of patients who have had and have recovered from an episode of myocardial infarction. It is conceivable, however, that ventricular aneurysm may be confused with other anatomic abnormalities, such as ventricular hypertrophy or aortic aneurysm, or may explain such findings as a systolic murmur or calcification in the heart.

The methods thus far employed in the attempt to detect these aneurysms during life have been those of physical, roentgen-ray and electrocardiographic examination. A critical evaluation of the entire subject and a review

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of the literature are given by Parkinson et al.[3] Rosenbaum et al.[4 and 5] have recently pointed out the remarkable frequency with which persistent displacement of the RS–T segment of the electrocardiogram may be associated with ventricular aneurysm. Rosenberg and Messinger[6] recently described Q waves and persistent RS–T segment elevations in the precordial leads of eight patients with anterior ventricular aneurysms. These observers pointed out that, of seven patients with ventricular aneurysm at autopsy, three did not show persistent RS–T elevation in the precordial leads.

Other efforts to utilize the electrocardiogram in the diagnosis of ventricular aneurysm have revealed the existence of several patterns in a varying percentage of cases. One consists of a downward major deflection of the QRS with inversion of T and an upright P wave in Lead I and an upright QRS in Lead III. Another type consists of QRS directed downward in II and III and upward in I.[7, 8] These studies were concerned with conventional leads only. Another study in which multiple unipolar leads were employed described an upward QRS in the unipolar right arm lead (aVR).[9]

None of the authors has made any claim for specificity of these patterns in aneurysm of the ventricle. Some authors have stressed this nonspecificity, and expressed the opinion that the electrocardiogram is of no value in the diagnosis except to indicate the presence and location of a healed myocardial infarct. Wilson et al.[5] suggested that persistent RS–T displacement was associated with ventricular aneurysm more often than one would expect on the basis of what is known concerning the frequency of the two phenomena, but then felt that this probably means simply that infarcts of the type which produce persistent RS–T displacements are in some respects like those that lead to ventricular aneurysm. Goldberger[9] noted the invariable association of an upright QRS complex in the unipolar right arm lead (aVR), and concluded that its absence eliminated the diagnosis of ventricular aneurysm. The present study is a reëxamination and elaboration of this problem.

Case Reports

Case 1. A 56 year old woman was first admitted to the Peter Bent Brigham Hospital September 15, 1945, in congestive failure. Although there was no evidence of acute myocardial infarction, and a series of electrocardiograms showed a static appearance, the diagnosis of acute myocardial infarction was made on the basis of the tracings shown in figure 1, A. There were low EMF, inverted $T_{I \text{ and } IVF}$ and slight left axis shift, and T_{IVF} was of coronary contour. On re-admission for congestive failure two years later the electrocardiogram (figure 1, B) showed a similar appearance in the conventional leads, while the unipolar limb leads showed a predominantly upright QRS complex in aVR with deep QS and elevated S–T in aVF; the unipolar chest leads showed elevated ST $_{V1-6}$, maximal in V_2, prominent Q $_{V4, 5}$ and late inversion of T $_{V2-6}$. The note was made that the tracing showed very little change over that taken during the presumed acute myocardial infarction, and the electrocardiographic diagnosis of ventricular aneurysm was suggested. An electrocardiogram taken during the terminal admission (figure 1, C) was essentially unchanged and S–T

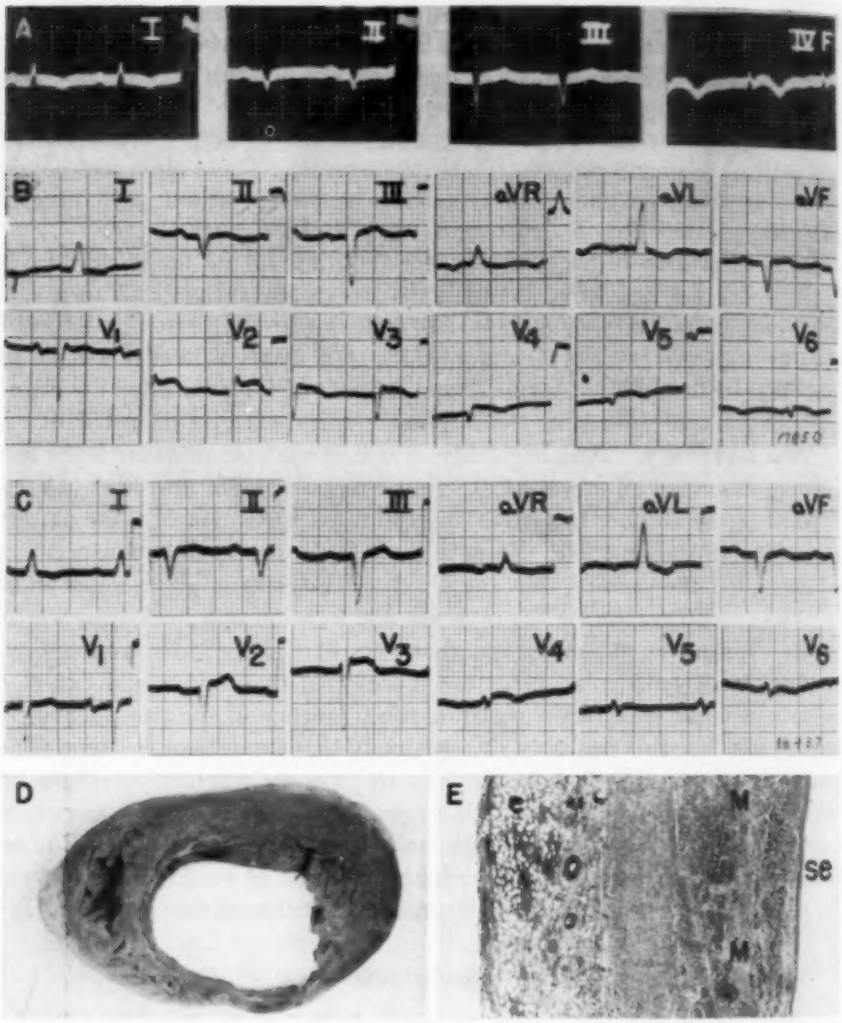

FIG. 1. Anteroseptal infarct with upright QRS in aVR and persistent RS-T segment elevation.

A. Conventional leads and IVF on first admission for congestive failure. The diagnosis of acute anterior myocardial infarction was made on the basis of T wave changes in I and IVF.

B. Tracing two years later during another admission for congestive failure, showing similar appearance in I–III and V_4 as well as correlative changes in aVR and the unipolar chest leads characteristic of acute anterior myocardial infarction. Ventricular aneurysm was suspected on the basis of persistent RS–T displacement.

C. Tracing five months later during final admission for another episode of congestive failure, showing no essential change.

D. Transverse section through heart midway between apex and base, showing aneurysmal thinning of anterior left ventricular wall.

E. Low power photomicrograph through thin wall of aneurysm, showing scattered islands of intact myocardium (m) near the subendocardium (se) and exudate in the epicardial tissue (e).

elevation was still present. The patient was not well enough for fluoroscopic examination. There was no evidence of ventricular aneurysm on physical examination. She died shortly after admission following pulmonary embolism.

At postmortem examination there was seen marked cardiac hypertrophy and healed anteroseptal infarct, resulting in marked thinning with aneurysmal bulging (figure 1, D). Microscopic examination through this thinned wall showed marked loss of myocardium, with a few scattered remnants of muscle at the junction of the middle and inner thirds of the aneurysm. The epicardium showed a low-grade inflammatory reaction, manifested by granulation tissue and scattered diffuse round cell infiltration (figure 1, E). There was no evidence of recent infarction.

In this case, it was probably an error to make the diagnosis of acute myocardial infarction at the time of the original admission. Electrocardiograms from then until the death of the patient showed an unchanging appearance, probably residual from an acute myocardial infarction which had occurred some time previously. It was only at the second admission that the possible responsibility of ventricular aneurysm for the electrocardiographic picture was recognized.

Case 2. A 61 year old psychotic male was admitted because of abdominal and low substernal pain, dyspnea, weakness, tachycardia and collapse. There was no history of hypertension or angina, and on no occasion had electrocardiograms been taken before the present admission. Physical examination revealed auricular fibrillation and evidence of congestive heart failure. Electrocardiograms (figure 2, A) showed auricular fibrillation, an abnormal form of ventricular complex (prominent Q_1 and elevated $S\text{–}T_{1,2}$), rsR in aVR, prominent Q with elevated S–T in aVL). The unipolar chest leads showed absent R and elevated S–T in $V_{1\text{–}6}$ and V_5 (ensiform lead) with late inversion of T $V_{2\text{–}7}$. These changes were interpreted as characteristic of massive anterior myocardial infarction, probably recent. He died suddenly 22 hours later.

Autopsy revealed marked thinning of the anterior wall of the left ventricle with definite outward bulging (figure 2, B). The very thin rim of myocardium in this wall showed, in addition, changes of recent infarction. The pericardium exhibited a low-grade pericarditis similar to that seen in the first case, and this was not located in relation to the recent infarct or to blood vessels (figure 2, C).

This is a complicated case in which the changes of acute myocardial infarction were superimposed on those of ventricular aneurysm, both the acute and chronic processes being in the same general area. Therefore, none of the facts available to the clinician could have enabled him to infer the existence of ventricular aneurysm. It would be conceivable, however, that an identical or similar pattern might have been obtained in the absence of acute infarction.

Case 3. A 67 year old woman was admitted in congestive failure. Several months previously she had been treated with morphine and prolonged bed rest for an obscure illness, but there was no history of previous chest pain and on no previous occasion were electrocardiograms taken. The physical examination at the time of her terminal illness revealed cardiac enlargement, gallop rhythm, a grade 2 systolic murmur over the precordium, pulmonary congestion and blood pressure of 130 mm.

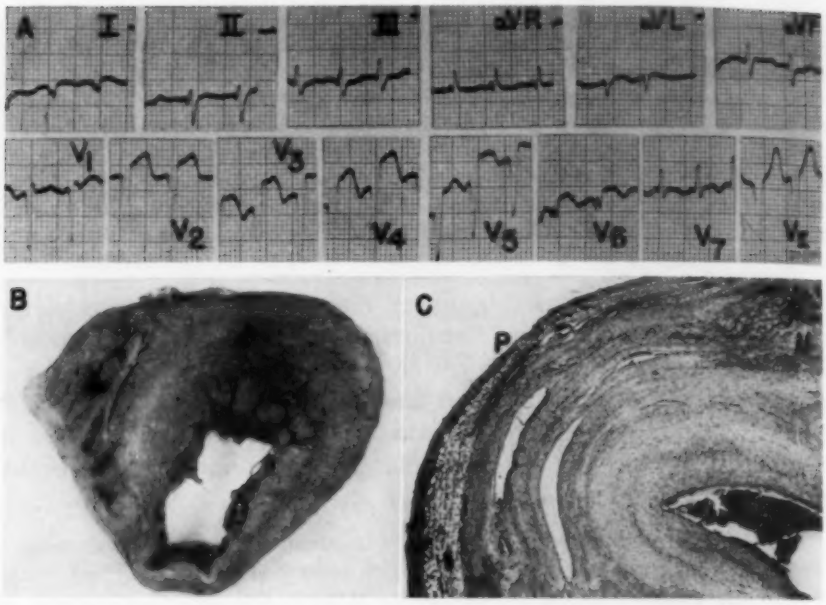

FIG. 2. Acute myocardial infarction within the aneurysmal wall.

A. Electrocardiogram taken during last day of terminal illness, showing auricular fibrillation, deep notched QS, elevated ST and late inversion of T_1, upright QRS_{aVR}, deep Q, elevated ST_{aVL}, deep Q and elevated ST_{V1-6} and late inversion of T_{V2-7}. This was regarded as characteristic of acute massive anterior myocardial infarction.

B. Transverse section of heart midway between apex and base, showing aneurysm of anterior wall of the left ventricle with fresh infarct in the wall of the aneurysm. The dark area posteriorly is artefact.

C. Low power photomicrograph, showing fibrous wall of aneurysm with patch of necrotic myocardium (m) and exudate immediately beneath the pericardium (p).

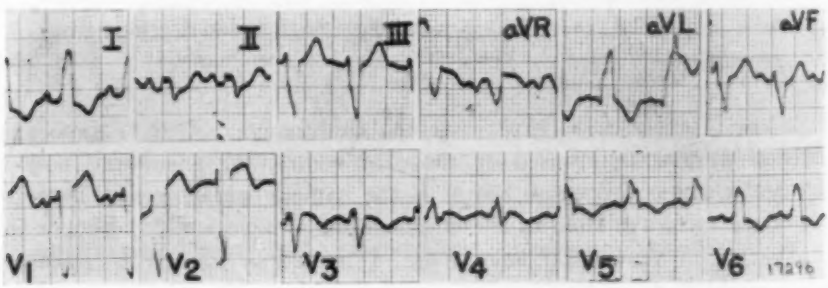

FIG. 3. Left bundle branch block with ventricular aneurysm. Tracing during terminal illness in congestive failure, showing left bundle branch block. Autopsy showed antero-apical aneurysm and scarring of the interventricular septum.

Hg systolic and 100 mm. diastolic. The electrocardiogram (figure 3) showed left bundle branch block. The patient died two days later.

Autopsy revealed an old antero-apical myocardial infarct with aneurysmal bulging and marked scarring of the interventricular septum. There was no recent infarction or pericarditis.

It is well known that left bundle branch block can obscure the changes of recent or old myocardial infarction. It would be impossible to state whether, in the absence of left bundle branch block, the pattern similar to that noted in other cases of the present group would have been inscribed. This was the only instance of left bundle branch block in this series.

Case 4. A 44 year old woman was admitted because of angina pectoris. Ten years previously she had had an episode of paroxysmal ventricular tachycardia associated with precordial distress and dyspnea lasting three weeks. A positive Wassermann reaction was discovered at that time and she was given antiluetic therapy over a five year period without serologic reversal. Physical examination showed a blood pressure of 143 mm. Hg systolic and 78 mm. diastolic. Fluoroscopic and roentgenkymographic examination showed a marked bulge with systolic expansion along the upper half of the left border of the left ventricle as viewed in the right anterior oblique and posteroanterior positions (figure 4, B). The electrocardiogram (figure 4, A) revealed flat T_1 and slightly inverted T in CF_{1-6}. Unipolar limb or chest leads were not obtained, but the calculated aVR showed a downward QRS. The patient was discharged to the care of her physician.

In this case the existence of ventricular aneurysm was well established by roentgenogram. The electrocardiogram did not reveal the persistent pattern of RS–T elevation seen in most cases of this group. Calculated aVR did not show the upward QRS pattern described by Goldberger.[9]

Case 5. A 66 year old man was admitted because of congestive failure. He had had precordial pain for the past eight months. Electrocardiograms had not been taken before the present admission. The electrocardiogram (figure 5) revealed an inverted T_1, deep broad Q_3, minimally elevated S–T_3, deep Q, and inverted T_{IVF}. Calculated aVR showed a downward QRS complex. The tracings were interpreted as indicating acute myocardial infarction. The patient died 17 hours after admission.

At autopsy the apex of the heart was the site of an old infarct with marked aneurysm formation 4 cm. in diameter, the wall of the aneurysm being thinned to 3 mm. There was no recent infarction and no pericarditis.

Although the electrocardiographic examination in this case was limited to the conventional leads and IVF, the same pattern of persistent RS–T displacement was obvious.

Case 6. A 73 year old man was treated in June 1946 for acute anterior myocardial infarction. A tracing taken one year previously showed only low T_1 and slight left axis deviation. Electrocardiograms (figure 6, A) at the time of the acute episode showed a small R in Lead I, deep notched QRS complexes in II and III, deep Q, absent R and moderately elevated S–T in CF_{2-4}, beginning terminal inversion of T in CF4, and biphasic T $_{CF5 \text{ and } 6}$. A week later there was some return of the elevated S–T segment in CF_{2-4} toward the isoelectric line, with definite terminal inversion of T $_{CF5-6}$ and in Leads I–III (figure 6, B). The patient was re-admitted on April 15, 1947, because of acute dyspnea and chest pain. The electrocardiogram (figure 6, C) showed return of the T waves to the upright direction in the standard leads. The unipolar leads taken for the first time showed an upright QRS in aVR. Unipolar chest leads showed return of T to an upright direction, with absent R in V1–6 and slight elevation of S–T in V2–6. This was considered characteristic of old anterior myocardial infarction. He died three days later.

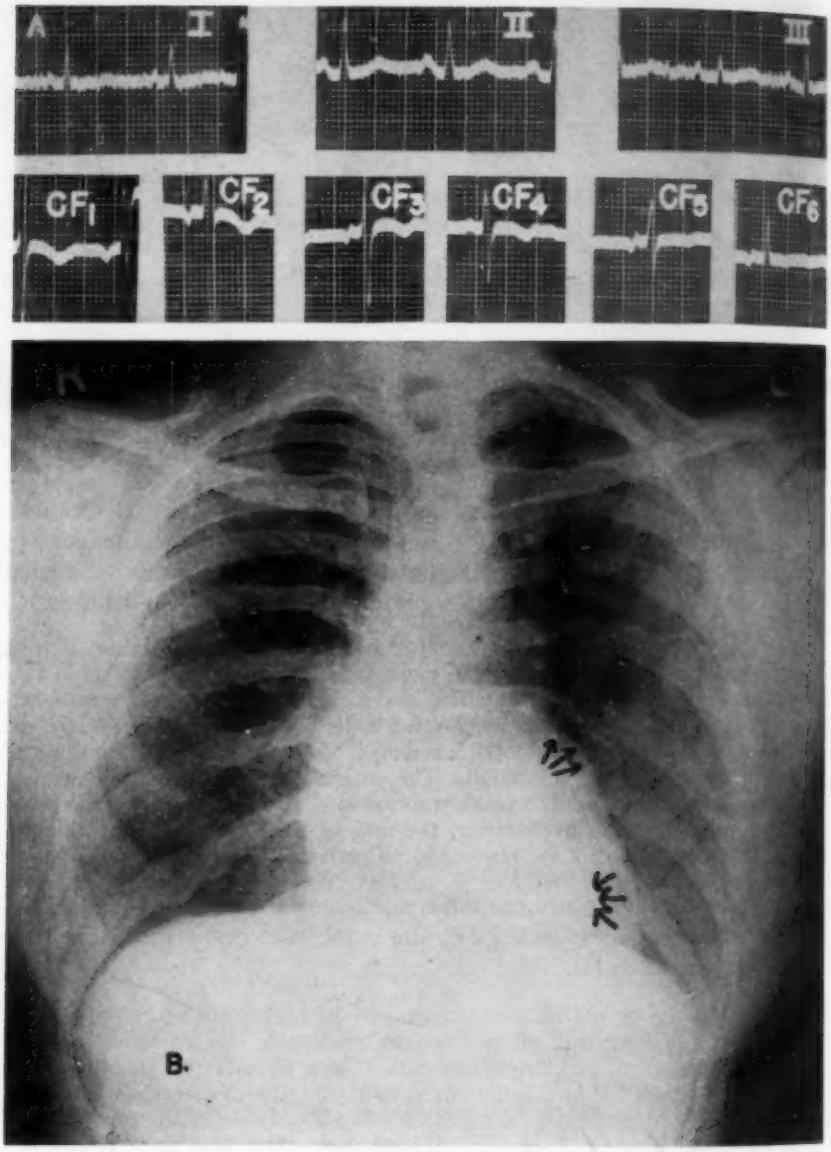

FIG. 4. Ventricular aneurysm detected roentgenographically with nonspecific electrocardiographic changes.

A. Electrocardiogram taken after diagnosis was made showing low T_1 and inverted T_{CF1-6}. The persistent RS–T displacement pattern was absent, and calculated aVR was downward.

B. PA teleroentgenogram with arrows illustrating paradoxical pulsation of ventricular aneurysm.

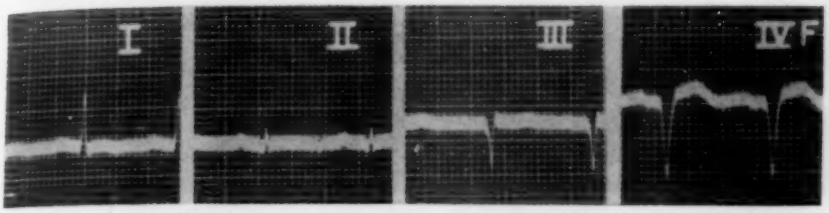

FIG. 5. Acute myocardial infarct pattern: ventricular aneurysm but no infarction found at autopsy. Tracing during terminal illness with congestive failure. Acute myocardial infarction was diagnosed on the basis of inverted T in I and IVF and elevated ST_{IVF}. Autopsy showed antero-apical aneurysm with no fresh infarct.

Autopsy revealed an old anteroseptal myocardial infarct, with aneurysmal bulging of the left ventricle measuring 5 cm. in diameter. There was no recent infarction or pericarditis.

In this case, electrocardiographic tracings were made thrice—one year before the acute infarction, during the acute episode, and 10 months later. During the acute episode they were typical of myocardial infarction. The final set of tracings, taken 10 months later, showed the residual changes in the same region of the heart as that affected during the acute episode. Except as an evidence of an old anterior myocardial infarction, these curves were not remarkable, showing only a slight degree of S–T elevation in association with deep QS in V2–6 and inversion of T in V5 only. Hence, in this case, the possibility of ventricular aneurysm was not suggested. Autopsy showed a fair sized aneurysm but no evidence of pericarditis on or near the aneurysm wall.

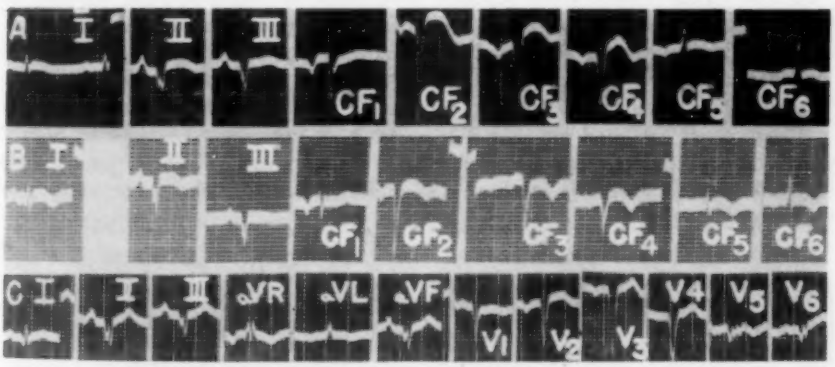

FIG. 6. Ventricular aneurysm showing upright QRS in aVR and persistent RS–T elevation over the precordium.

A. Tracing taken during acute episode of myocardial infarction showing small R_1, $QS_{2, 3}$, absent R and elevated ST_{CF2-4}, with beginning terminal inversion of T_{CF6} and biphasic $T_{CF5, 6}$.

B. One week later, tracing showing some return of elevated ST toward isoelectric in CF 2–4, with definite terminal inversion of T in CF 2–6 and also in Leads I–III.

C. Electrocardiogram taken 10 months later, during the terminal illness with dyspnea and chest pain. Lead aVR, taken for the first time, showed a predominantly upward QRS. The unipolar chest leads showed absent R_{V1-6} and slightly elevated ST_{V2-6}. This was considered characteristic of old anterior myocardial infarction. Autopsy revealed an anterior ventricular aneurysm.

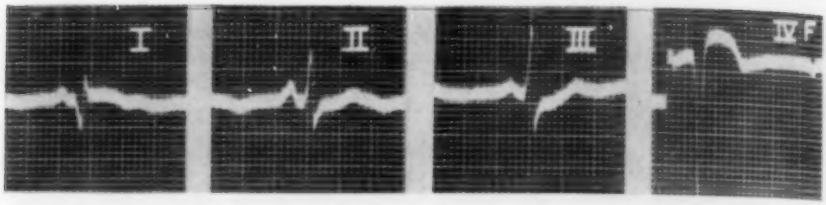

FIG. 7. Ventricular aneurysm diagnosed by roentgenogram and by physical examination. Tracing shows elevated ST and prominent Q in I and IVF during a period when there was no evidence of active myocardial infarction. Fluoroscopy confirmed an anteroapical ventricular aneurysm.

Case 7. This patient (also reported by Fulton [10]) was a 55 year old man who had a typical anterior myocardial infarction in 1936 and was admitted in November, 1938, when the diagnosis of ventricular aneurysm was made by the finding of a "heaving, discrete, double impulse seen and felt in the fourth interspace over the nipple," and by the fluoroscopic demonstration of paradoxic pulsation of an apical bulge. Review of the electrocardiogram (figure 7) shows a prominent Q and elevated S–T in I and IVF persistent over a three-day observation period. Calculation showed a flat QRS in aVR. There was no clinical evidence of acute myocardial infarction.

In this case the diagnosis of ventricular aneurysm was made by physical examination and confirmed fluoroscopically. Reëxamination of the electrocardiograms showed a pattern characteristic of acute myocardial infarction, but presumably persistent from the time of the acute infarct two years previously.

Case 8. This patient (also reported by Fulton [10]) was a 55 year old man who had an acute myocardial infarction in 1933 with subsequent recurring angina. Physical examination revealed a forceful thrust in the fourth interspace above the nipple. Ventricular aneurysm was diagnosed at fluoroscopy from the paradoxic pulsation of a posteroapical bulge of the left ventricle. The electrocardiogram (figure 8) showed depressed S–T and biphasic T_1, inverted T_2, prominent Q, elevated S–T and inverted T_3, depressed S–T and biphasic T_{IVF}. Calculated aVR showed a downward QRS. The patient is reported to have died suddenly several years later; autopsy was not performed.

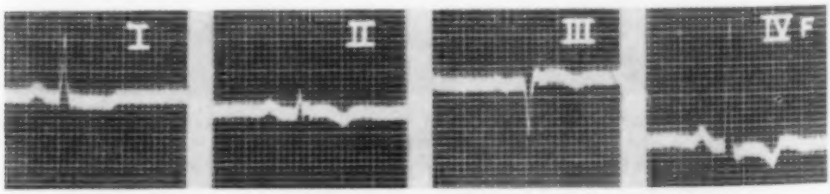

FIG. 8. Ventricular aneurysm diagnosed by roentgenography. Tracing shows depressed ST and biphasic T_1, inverted T_2, prominent Q, elevated ST, and inverted T_3, depressed ST and biphasic T_{IVF}. The aneurysm was situated in the posteroapical portion of the left ventricle.

This was the only instance of posterior ventricular aneurysm in this series, the diagnosis being made by fluoroscopy. At this time the patient presented no clinical evidence of acute myocardial infarction, yet the electrocardiogram, in addition to the finding of left ventricular hypertrophy, showed changes (deep Q, elevated S–T, and inverted T_3) which ordinarily are regarded as characteristic of acute posterior myocardial infarction. It seems reasonable that in this case, as in those described above, this pattern was fixed over a long period of time. This suggests that, just as persistent changes of acute anterior myocardial infarction may be seen in ventricular aneurysm of the anteroapical region, persistent changes of acute posterior myocardial infarction may be seen with ventricular aneurysm of the posteroapical region of the heart.

Case 9. The patient was a 65 year old slate worker who had suffered an acute myocardial infarction in 1946. He was seen eight months later in April, 1947, because of dyspnea and chest pain. At that time ventricular aneurysm was diagnosed from a forceful bulge synchronous with ventricular systole, seen and felt just within the left border of cardiac dullness near the apex, and considered to be rather inconsistent with the normal blood pressure. The electrocardiogram at that time showed changes quite characteristic of acute myocardial infarction, with elevated S–T in I, aVL and V1–4, deep Q $_{V1-4}$, and inverted T $_{V1-6}$. Fluoroscopy showed a paradoxic outward expansion in the region of the apex synchronous with contraction of the rest of the ventricular shadow. These findings were regarded as convincing evidence of ventricular aneurysm. The physical examination remained essentially unchanged during the following 16 months until he was re-admitted for congestive heart failure, which responded satisfactorily to conventional therapy. Figures 9, A and 9, B show the appearance of the electrocardiograms in August, 1947, and July, 1948, respectively, and are quite similar to those seen in April, 1947. Figure 9, C is a right anterior oblique roentgenogram of the chest showing the abnormal protuberance. On the last admission this was again demonstrated, but paradoxic pulsation could not be shown.*

In this case the time relationships are quite clear-cut. The acute myocardial infarct developed in 1946, and characteristic physical and roentgenographic signs of ventricular aneurysm were demonstrated eight months later. Two years after the infarction a fluoroscopic examination was equivocal, although the physical examination was very suggestive of ventricular aneurysm and the electrocardiographic pattern characteristic of acute myocardial infarct involving the anteroseptal portion of the left ventricle remained constant.

Case 10. A 77 year old retired salesman had an acute myocardial infarction in November, 1943. The electrocardiogram (figure 10, A) showed inverted T in I and IVF and elevated S–T in IVF. He did fairly well until January 3, 1946, when he was admitted because of chest pain. The clinical episode resembled an acute pneumonia, but the electrocardiogram demonstrated the changes of an acute myocardial

* In March 1949 the electrocardiogram showed the characteristic changes of right bundle branch block. The patient died in April 1950. Autopsy showed a tremendously enlarged heart with a huge anterior aneurysm. Laminated thrombi were attached to and filled the aneurysmal sac.

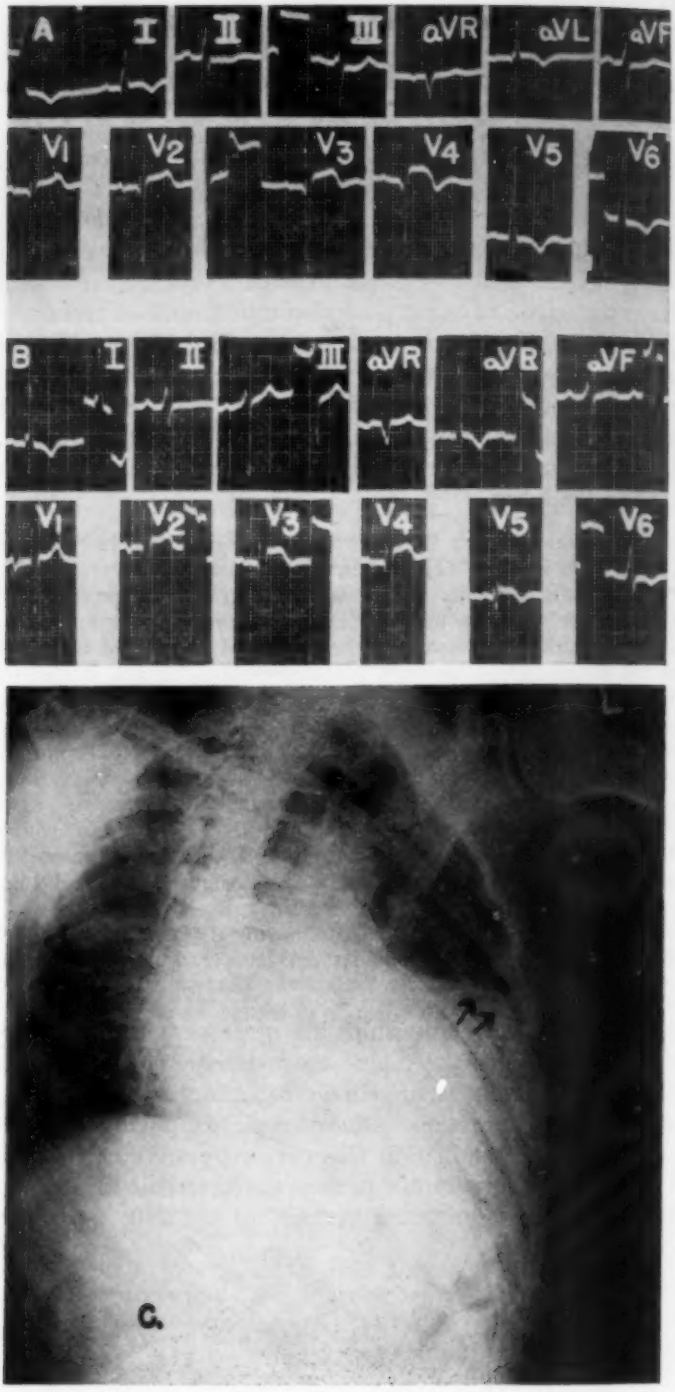

FIG. 9. Ventricular aneurysm diagnosed by physical examination and confirmed by roentgenogram. Acute myocardial infarction in 1946.

A. Tracing taken August, 1947, showing changes typically seen in acute anterior myocardial infarction, but there was no clinical correlation of this.

B. Tracing taken July, 1948, with essentially similar appearance. QRS in aVR was downward.

C. Roentgenogram in the right anterior oblique position, showing abnormal protuberance on the left border of the heart near the apex.

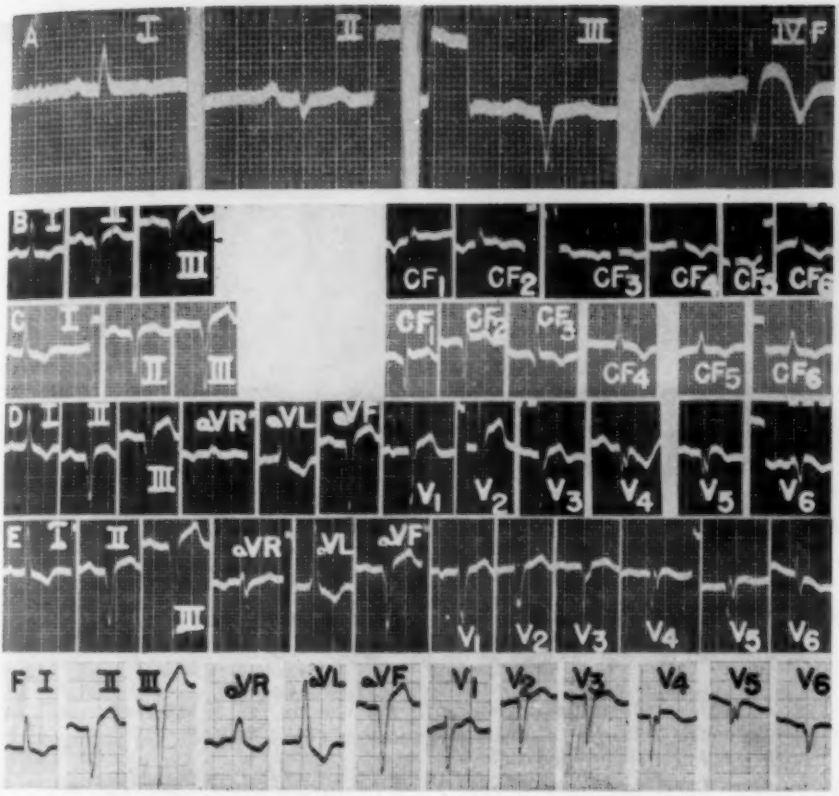

FIG. 10. Ventricular aneurysm suggested electrocardiographically and confirmed roentgenographically.

A. Tracing taken during acute myocardial infarction, showing inverted $T_{1 \text{ and IVF}}$ and elevated ST_{IVF}.

B. Tracing three years later, during episode of "pneumonia," showing no change in standard leads and deep Q_{CF1-4} and elevated ST_{CF1-6} with inverted T_{CF3-6}.

C. Electrocardiogram during similar clinical episode, showing no change.

D. Four months later, during acute pulmonary edema, when unipolar leads were used for the first time. QRS in aVR was predominantly upright. There was a deep Q, elevated ST_{V1-6} and inverted T_{V2-6}.

E. Similar episode four months later, showing change to rS in aVR but no other essential change. This was regarded as evidence of myocardial infarction of uncertain duration at this time.

F. Tracing during last admission, showing upright QRS in aVR and no other essential change. At this time the diagnosis of ventricular aneurysm was suggested by the electrocardiographer.

infarction (figure 10, B). In October, 1946, he was again admitted with a similar clinical syndrome and a similar electrocardiographic picture (figure 10, C). In January, 1947, he was re-admitted in acute pulmonary edema, and the electrocardiogram (figure 10D) showed no essential change. At this time unipolar leads were taken, and aVR showed an M-shaped QRS complex, deep Q, elevated S–T $_{V1-4}$, W-shaped QRS in V4–5, and a suggestion of terminal inversion of T $_{V2-6}$. The change from bipolar to unipolar leads may account for some of the changes seen. In August, 1947, another episode of acute pulmonary edema necessitated re-admission,

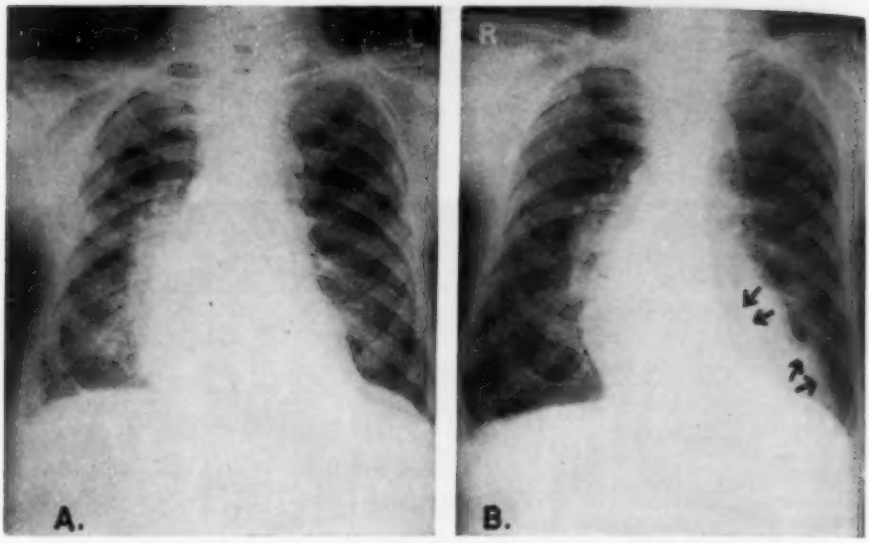

FIG. 11. Same case as figure 10.

A. P.A. teleroentgenogram of the heart taken at the same time as tracing E (figure 10), showing merely generalized cardiac enlargement and engorged hilar vessels.

B. P.A. film, taken at suggestion of electrocardiographer during the last admission, showing abnormal bulge at the apex of the left ventricle.

and on the basis of the electrocardiogram (now showing an RS pattern in aVR) the infarct was considered to be of uncertain duration (figure 10, E). A roentgenogram of the chest showed generalized cardiac enlargement to the right and left with engorgement of the hilar vessels (figure 11, A). In December, 1947, the patient was re-admitted for a possible renal infection. At this time the diagnosis of ventricular aneurysm was finally suggested because of persistent S–T segment displacement. The electrocardiogram (figure 10, F) showed QRS 0.10 second, PR 0.20 second, elevated ST in II, III, aVF, and VI–6, decreasing R V_{1-6}, deep Q V_1, QS $V_{5,6}$, R pattern in aVR. On this clue, fluoroscopic examination was repeated and now showed a rounded prominence of the left ventricle projecting anteriorly and showing systolic expansion, confirming the suspicion of ventricular aneurysm (figure 11, B). The patient is alive at this writing.

In this case the persistent electrocardiographic pattern, characteristic of that seen in acute myocardial infarction but not changing significantly over several observations, repeatedly raised the question of recurrent myocardial infarction. However, in each subsequent episode some condition other than acute infarction was established, viz., bronchopneumonia, acute pulmonary edema, etc. Eventually the suspicion of ventricular aneurysm was aroused on the basis of the persistent S–T segment elevation, and the diagnosis was substantiated by roentgenography. It is of some interest that in this case the QRS complex in lead aVR changed from entirely upright (RR′) to biphasic (RS) in direction. This suggests that a stable electrical state with an inevitably upright QRS complex in aVR is not necessarily present in ventricular aneurysm.

Discussion

In the present series of 10 ventricular aneurysms, proved fluoroscopically or pathologically, both of the electrocardiographic patterns (upright QRS_{aVR} or persistent elevation of RS–T) were found in an overwhelming majority of cases. An attempt was made in this limited group to determine the relative value of an upright QRS in aVR and persistent displacement of the RS–T segment. Unfortunately, aVR was recorded in only five of our cases, but in the others was calculated on the basis of the formula $(VR = (I + II)/2)$.[11] Because Leads I and II were not actually recorded simultaneously, this calculation must be regarded as gross and only an approximation. If case 3 is omitted from this consideration because of left bundle branch block, it is clear from chart 1 that while eight of nine cases showed a persistent S–T displacement, only four of nine showed an upward QRS in either a recorded or calculated aVR. The number of cases considered is obviously too small to warrant a definite conclusion regarding the relative

Chart I

Electrocardiographic-Pathologic Correlations in 10 Cases of Ventricular Aneurysm

Cases	QRS in aVR	Persistent RS-T Displacement	Pericarditis	Location of Aneurysm	Method of Diagnosis
1	Upright (recorded)	Present	Present	Antero-apical	Pathologic
2	Upright (recorded)	Present	Present	Antero-septal	Pathologic
3	Down (recorded)	Present (LBBB)	Absent	Antero-apical	Pathologic
4	Down (calculated)	Absent	—	Antero-basal	X-ray
5	Down (calculated)	Present	Absent	Apical	Pathologic
6	Upright (recorded)	Present	Absent	Antero-septal	Pathologic
7	Flat (calculated)	Present	—	Antero-apical	X-ray
8	Down (calculated)	Present	—	Postero-apical	X-ray
9	Down (recorded)	Present	—	Antero-apical	X-ray
10	Upward (recorded)	Present	—	Anterior	Pathologic

value of the two patterns, but it does suggest that the QRS_{aVR} pattern is no more accurate than the persistent RS–T pattern and, further, that the absence of the upright QRS in aVR does not eliminate the possibility of ventricular aneurysm.[9]

From a survey of the literature of the past 20 years,[2, 3, 7, 8, 9, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23] we have collected 55 well substantiated cases of ventricular aneurysm in which electrocardiographic tracings were published or adequate descriptions given of the electrocardiograms taken during a period following recovery from myocardial infarction. Forty-five of the 55 cases showed elevated S–T segments in a period when there was no evidence of another acute myocardial infarction. Adding the nine cases with persistent S–T elevation in our present series of 10 cases, it will be seen that 84 per cent of the cases with ventricular aneurysms under study presented this electrocardiographic finding.

In addition to confirming the frequent association of either of these pat-

terns with ventricular aneurysm, the present study also suggests that the existence of a persistent RS–T displacement may lead to the suspicion (cases 1 and 10), if not to the diagnosis, of ventricular aneurysm. This does not mean that the diagnosis will be confirmed in every case in which a persistent RS–T pattern is noted. A parallel study of persistent RS–T displacement in general was not attempted.

Displacements of the RS–T segment occurring during acute myocardial infarction have been explained as the result of currents of injury and the presence of nonpolarizable boundaries which define differences in magnitude of change of transmembranal voltage produced by the excitatory process. These displacements are transient and generally return to the isoelectric line within two weeks. The cause of persistent RS–T displacement is not clear. In some cases it can be explained as the result of so-called overlapping, that is (as in ventricular hypertrophy and bundle branch block), the repolarization process commences in some parts of the myocardium before the depolarization process has been completed in others. In other cases, especially those with a short PR interval, they may be attributed to the presence of the auricular T wave following immediately after the QRS complex.

The cause of this persistent S–T elevation in many cases cannot be explained in either way. On theoretic grounds one can hardly attribute persistent RS–T displacements to persistent nonpolarizable boundaries of the type described above; these boundaries are rapidly obliterated by the recovery, demarcation or death of the injured muscle. Katz,[24] however, attributes the persistence of the contour of acute myocardial infarction to chronic coronary insufficiency, ascribing the continued displacement to the presence of focal injured (not dead) areas of heart muscle. He infers that in those instances in which anatomic changes cannot be demonstrated, continued ischemia may account for these patterns. Many of the tracings published by him as examples of chronic coronary insufficiency resemble those observed in the present series of ventricular aneurysm, and one would assume that on this basis the latter would be regarded as examples of chronic coronary insufficiency.

There are several difficulties in the way of accepting this explanation for the changes in ventricular aneurysm. In the first place, with the exception of those cases with frank supervention of acute myocardial infarction (e.g., case 2), anatomic evidence of myocardial necrosis is lacking. If, lacking this anatomic proof, one would invoke myocardial ischemia as the cause of these changes, one would expect that ischemic changes alone should, on rest, be proved capable of regression, whereas the changes seen in Katz's group of coronary insufficiency and in these cases of ventricular aneurysm were quite fixed. Moreover, if one postulated ischemia as the cause of the changes in either group, one would have to assume that the elevated S–T segments seen in the precordial leads are the result of either *subepicardial* or

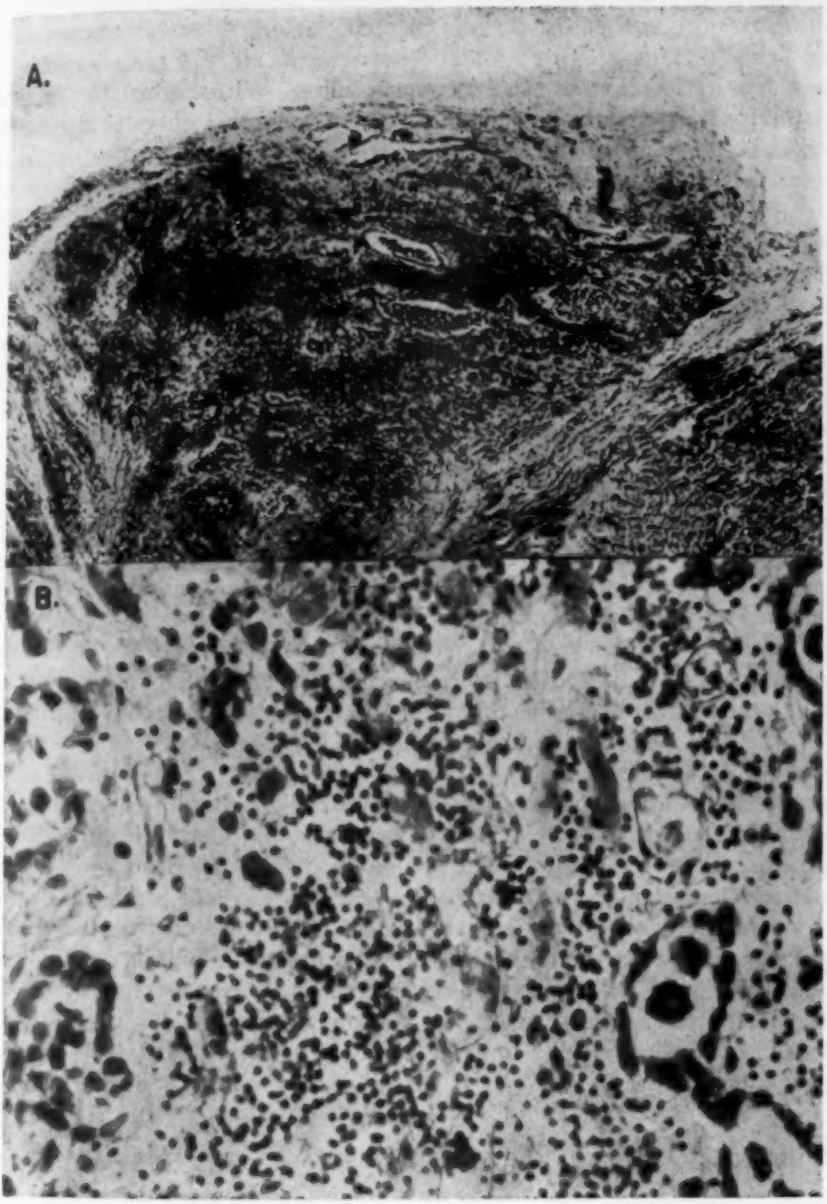

FIG. 12. Photomicrograph of exudative reaction in epicardium overlying ventricular aneurysm.

A. Low power field showing general distribution of exudate.
B. High power detail showing the cells to be lymphocytic and monocytic in type.

subendocardial ischemia. As to the former possibility, subepicardial ischemia is quite unusual in chronic coronary artery disease, current experience being that induced or spontaneous ischemia, in the great majority of cases, has its location in the subendocardium. With regard to the latter possibility, it is conceivable (though not proved) that there is a *subendocardial* ischemia in these cases of ventricular aneurysm, that there is an elevated RS–T segment in the ventricular cavity, and that this cavity potential is transmitted through the window formed by the wall of the aneurysm to the precordium. Most ventricular aneurysms, being situated in the left ventricle, are not accessible to catheterization, a procedure which at best would be considered dangerous in coronary artery disease and especially in ventricular aneurysm. In the absence of the data that might be obtained in this way, our knowledge must be regarded as incomplete on this point. The fact that the unipolar right arm lead (aVR) to which in a general way, the cavity potential is reflected did not show an elevated RS–T segment casts some doubt on this possibility. The electrical contribution made by the remaining myocardial fibers in the aneurysmal wall is unknown, and whether the electrical deviations noted in these cases are due to changes in the latter is a matter for speculation.

It is of some interest that, of the 10 cases of ventricular aneurysm examined at post mortem at the Peter Bent Brigham Hospital over the past three years (four of which, lacking electrocardiograms, are not included in the present series), microscopic evidence of a chronic inflammatory reaction in the pericardium overlying the aneurysm was found in seven (figure 12). We have been puzzled about the cause and significance of this finding. A pericarditis could conceivably be due to the constant trauma caused by the impact of the aneurysmal sac with the anterior chest wall. It is quite well known that pericarditis is capable of producing an elevation of the RS–T segment. Some hold that this reaction is due to the injury of the immediately underlying myocardium, but this point is still argued. Regardless of the mechanism of this change, it might be held that the RS–T segment elevation is due to the chronic pericardial reaction and the deep Q waves to the cavity potential's being transmitted through the aneurysmal wall to the precordium. Since this change was not observed uniformly in the present series of cases, the evidence must be regarded as merely suggestive.

Summary

Ventricular aneurysm, an occasional sequel to a very common disease, is frequently associated with the electrocardiographic appearance usually interpreted as evidence of acute myocardial infarction. But with ventricular aneurysm this appearance is noted over an unduly protracted period. Except in one instance, acute infarction was not associated with ventricular aneurysm at autopsy. In the present study the electrocardiographic finding of persistent RS–T displacement was noted more frequently than other electro-

cardiographic changes described as occurring with ventricular aneurysm. Although nonspecific, this finding should lead the clinician to suspect the existence of ventricular aneurysm. The mechanism of this phenomenon is unknown.

Addendum

In the first of five communications which have appeared or come to our attention since this article was written Myers and his colleagues,[25] correlating the electrocardiographic and pathologic findings in four patients with large antero-lateral infarcts, considered that the abnormal RS–T segments and T waves probably represent the endocardial aspect of activation of a hypertrophied left ventricular wall transmitted through the aneurysm, without modification when the wall is completely replaced by fibrous tissue, or with slight modification when it contains muscle remnants capable of activation and repolarization. With this suggestion in mind we have reëxamined our material from the standpoint of the existence of ventricular hypertrophy. In this group the patient was hypertensive in two, normotensive in two and borderline in one of five non-fatal or non-autopsied cases. Of five autopsied cases four showed left ventricular hypertrophy; the left ventricle of the fourth individual, the patient with left bundle branch block, was of normal thickness. Although a final answer to this problem is not at hand, the present data seem most consonant with the above expressed ideas of Gordon Myers. Moyer and Hiller,[26] in a recent publication, accept this explanation without reservation. Soulie, Laham and Papanicolis [27] discounted the chronic pericarditis, constantly observed in autopsies of parietal aneurysms, as a cause of the persistent RS–T displacements, but suggested rather that an inflammatory zone, which they assume to exist at the limits of the aneurysm, may be responsible for this phenomenon.

Although the Q–T interval of the electrocardiogram may be prolonged for other reasons than myocardial ischemia, it is generally considered [28] that myocardial ischemia should be associated with prolongation of the Q–T interval. Using Bazett's formula we have calculated the value for K in all cases excepting the patient with left bundle branch block. In one case the value was 0.34, in two 0.38, two 0.42, two 0.44, one 0.45 and one 0.47. The latter was the patient with recent as well as old infarction. It is clear then that ventricular aneurysm was not necessarily associated with a prolongation of the Q–T interval. This is indirect evidence against ischemia as a cause of the electrocardiographic changes.

In a noteworthy and original approach to the subject of ventricular aneurysm Lowe and Love [29] attempted a mechanical analysis of the factors responsible for aneurysm formation based upon the established anatomical structure of the ventricular wall, the properties of cardiac muscle and the physical nature of infarcted cardiac muscle. Their assumptions were substantiated by the finding of a close correspondence between the theoretical deformations of the ventricular wall and those occurring naturally. A possible relationship between these mechanical features and the electrocardiographic findings has not been investigated.

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HYPERTENSION IN OLDER AGE GROUPS *

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Many patients first found to have an abnormal elevation of the blood pressure after the sixth decade exhibit a much milder clinical picture than that usually associated with hypertensive vascular disease. Although it has been traditional to state that this disorder increases in incidence with advancing years, some workers have presented considerable evidence that the onset occurs at an early age.[1, 2, 3, 4] If essential hypertension begins in youth and early adult life, then the question may be raised whether the hypertension arising in later life is indeed the same process.

Studies of blood pressure as casually recorded have indicated generally an increase in the level of mean systolic pressure with age.[5, 6] This has been attributed principally to a reduction in elasticity of the aorta due to arteriosclerotic changes. The loss of elasticity of the great vessels theoretically should result in a lowering of diastolic pressure. However, Master and his associates,[5] in an unselected group of 14,849 men and women above the age of 40, and Russek and Zohman,[6] in a series of 3,691 men, found an increasing incidence of diastolic pressures greater than 95 mm. of mercury in increasing age groups. Zeman and Schwartz,[7] in a study of 150 cases over the age of 60, concluded that the level of the blood pressure in old age should not be taken as an index of the pathologic involvement of the vascular system.

Because of the controversial points raised by previous studies, it seemed desirable to secure data to determine whether the hypertension first recorded in the sixties and seventies constitutes a mild form of hypertensive vascular disease or is merely the result of an independent vascular degenerative process.

Clinical Material

Forty-four cases (series 1), selected from the autopsy files of the Presbyterian Hospital, fulfilled the following criteria: All had died after the age of 60, had previously exhibited repeated blood pressure readings of 160 mm. Hg systolic and 90 mm. diastolic or over, and, as far as could be determined by careful examination of their hospital records, hypertension had been discovered only after the age of 55. Subjects who had evidence of primary renal disease, pheochromocytomata, coarctation of the aorta, central nervous system or endocrine disease were excluded from the series.

Series 2 consisted of 18 cases secured from the same source. All of

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these had documented hypertension, with repeated elevation of blood pressure to 160 mm. Hg systolic and 90 mm. diastolic or over, and had died before the age of 55 of causes other than those usually considered complications of hypertensive vascular disease, i.e., congestive failure, myocardial failure, cerebral vascular accident or renal insufficiency. Again, those subjects with other conditions known to lead to hypertension were excluded.

Both series were made up of patients whose deaths occurred over approximately the same period of years. The pathologic data which were obtained from the description of the examining pathologist were considered comparable. The microscopic sections were reviewed in all those situations in which the descriptions were inadequate or open to question. From this material, the degree of arteriosclerosis was graded zero, minimal, moderate or advanced as determined by the examination of two to four sections of the kidneys. Data concerning headache, congestive failure, cardiac pain and retinitis were obtained from the hospital records of the subjects. It was not possible in all cases to establish the exact age of onset of elevated blood pressure, hence age at time of diagnosis was recorded.

Results

The detailed observations of each patient are recorded in tables 1 and 2, and the two series summarized in table 3.

The average duration of known hypertension in both groups was comparable, 4.6 years in series 1 and 5.9 years in series 2. Whereas the sex incidence showed a preponderance of males in the group of elderly patients, there was an equal number of men and women in the younger series. Headaches as a symptom associated with hypertension were about two and one-half times as common in the younger series. Findings such as heart weight and thickness of the left ventricle were not significantly different in the two groups.

The most striking difference in the two series was seen in the incidence of moderate or advanced renal arteriolosclerosis as determined at autopsy. In the group of elderly hypertensives, significant arteriolar damage in the kidney was present in 31.8 per cent, contrasted with 72.2 per cent in the younger group.

Discussion

The comparison of a group of elderly and younger hypertensives reveals primarily a greater incidence and degree of arteriolosclerosis in the renal area of the younger group. This observation is apparent even though data concerning the two series of patients were obtained under essentially similar conditions and the antecedent duration of known hypertension was comparable in the two groups.

The validity of this difference is strengthened by the undoubted inclusion in the series of elderly patients of some individuals with true hypertensive vascular disease whose abnormal elevation of blood pressure may

TABLE I

Clinical and Pathologic Data of 44 Patients Whose Hypertension Was First Recognized After the Age of 55

No.	Sex	Age Diag. High B.P.	Age at Death	Highest B.P.	Head-ache	Cong. Failure	Cardiac Pain	Cerebral Accident	Retinal Changes	Heart Wgt. gm.	Max. Left Vent. Thickness cm.	Coronary Arterio-sclerosis	Aortic Arterio-sclerosis	Renal Arteriolo-sclerosis	Other Arteriolo-sclerosis
1	M	57	60	200/118	0	0	0	0	+	380	1.7	+	+	0	0
2	F	61	61	190/120	+	0	0	+	+	500	1.5	+	+	min.	min.
3	M	61	61	170/120	+	0	0	0	+	620	2.0	+	+	mod.	mod.
4	F	61	62	200/110	+	+	0	0	+	340	1.7	0	+	0	min.
5	M	61	62	240/150	0	+	+	0	++	500	1.9	+	+	min.	min.
6	F	59	62	190/110	0	+	0	0	?	310	2.0	0	+	min.	min.
7	M	63	63	200/100	0	0	+	+	+	620	2.0	+	+	min.	min.
8	M	56	63	195/120	0	0	+	0	0	480	1.8	+	+	min.	min.
9	M	63	63	170/110	0	+	+	0	+	420	2.0	+	+	min.	min.
10	M	60	64	240/140	0	0	0	0	?	400	2.0	+	+	min.	min.
11	F	62	64	170/110	+	+	+	0	+	400	1.5	+	+	0	min.
12	M	63	64	240/140	0	+	0	0	?	560	2.3	+	+	adv.	adv.
13	F	63	66	250/100	0	0	+	0	0	340	1.7	+	+	0	min.
14	M	63	66	190/110	0	+	0	0	?	300	1.3	+	+	min.	min.
15	M	60	66	240/160	0	+	0	0	+	760	1.9	+	+	adv.	min.
16	M	60	67	190/110	0	0	0	0	?	420	2.2	+	+	min.	min.
17	M	60	67	220/130	0	0	0	0	+	420	2.0	+	+	adv.	mod.
18	M	67	67	210/118	0	0	0	0	?	460	2.0	0	+	min.	min.
19	F	58	68	215/155	+	+	+	0	+++	360	1.0	+	+	mod.	mod.
20	M	69	69	180/110	0	+	+	0	0	340	2.0	+	+	mod.	mod.
21	F	66	69	180/110	0	+	0	0	?	380	2.0	+	+	mod.	mod.
22	M	69	70	190/110	0	0	0	0	?	300	1.6	+	+	0	0

TABLE I—*Continued*

No.	Sex	Age Diag. High B.P.	Age at Death	Highest B.P.	Head-ache	Cong. Failure	Cardiac Pain	Cerebral Accident	Retinal Changes	Heart Wgt. gm.	Max. Left Vent. Thickness cm.	Coronary Arterio-sclerosis	Aortic Arterio-sclerosis	Renal Arteriolo-sclerosis	Other Arteriolo-sclerosis
23	M	70	70	174/96	0	0	0	0	?	420	1.2	+	+	0	min.
24	M	70	70	160/110	0	+	+	0	?	400	1.5	+	+	0	min.
25	M	60	71	220/110	0	+	+	0	+	320	1.7	+	+	mod.	mod.
26	F	63	71	210/115	0	+	0	0	+	700	1.9	0	+	adv.	min.
27	M	67	72	222/120	+	+	+	0	+	?	1.4	0	+	adv.	mod.
28	M	69	73	210/140	0	+	0	0	+	340	1.5	+	+	min.	min.
29	F	73	73	220/120	0	+	+	+	?	340	1.4	+	+	min.	mod.
30	F	69	74	220/110	0	+	0	+	+	480	2.2	+	+	min.	min.
31	F	59	74	200/90	+	+	0	0	+	480	1.3	0	+	0	min.
32	M	63	74	200/110	0	+	0	0	+	480	2.0	+	+	min.	min.
33	M	75	75	190/90	0	0	0	0	?	470	1.5	+	+	min.	min.
34	F	77	77	226/120	0	0	0	0	?	260	1.3	0	+	0	0
35	M	73	79	210/120	0	0	0	0	?	400	1.6	+	+	min.	min.
36	F	73	79	180/110	0	0	0	0	?	290	1.5	0	+	0	min.
37	F	60	80	224/120	0	+	0	+	+	480	1.8	+	+	min.	min.
38	F	80	80	190/90	0	+	0	0	?	500	1.5	+	+	min.	min.
39	M	76	80	200/110	0	+	+	0	?	400	2.0	0	+	0	min.
40	F	71	81	230/120	0	0	+	+	0	420	1.8	+	+	mod.	mod.
41	M	79	82	220/90	0	0	+	0	+	380	1.9	0	+	min.	min.
42	F	62	83	190/110	0	+	0	0	?	530	2.0	+	+	mod.	mod.
43	F	85	85	210/100	+	0	0	0	?	360	2.2	+	+	mod.	min.
44	M	78	88	210/112	0	0	0	0	?	440	1.3	+	+	mod.	min.

TABLE II

Clinical and Pathologic Data of 18 Patients with Hypertensive Vascular Disease Who Died of Other than the Usual Complications

No.	Sex	Age Diag. High B.P.	Age at Death	Highest B.P.	Head-ache	Cong. Failure	Cardiac Pain	Cerebral Accident	Retina	Heart Wgt. gm.	Max. Left Vent. Thickness cm.	Coronary Arterio-sclerosis	Aortic Arterio-sclerosis	Arteriolo-sclerosis		Cause of Death
														Renal	Other	
1	F	33	41	250/160	+	0	0	0	+	500	2.0	0	0	adv.	adv.	Leukemia
2	F	40	42	220/120	+	0	0	0	0	320	2.0	0	0	0	0	Lymphosarcoma
3	F	41	46	220/115	+	0	0	0	?	400	1.9	+	+	mod.	mod.	Ca. pancreas
4	F	47	48	200/110	+	+	+	0	+	220	2.0	0	0	mod.	mod.	Ca. esophagus
5	F	42	48	220/120	0	0	0	0	?	370	2.0	0	+	min.	mod.	Sarcoma
6	F	48	49	225/140	0	0	0	0	?	380	1.7	+	+	mod.	mod.	Lobar pneumonia
7	M	49	49	180/136	+	+	0	0	?	520	1.5	0	+	min.	0	Silicosis
8	M	40	49	215/140	+	0	0	0	++	420	1.5	+	+	mod.	min.	Ruptured aneurysm
9	M	30	50	210/100	?	?	?	?	?	680	2.0	+	+	mod.	mod.	Dissect. aneurysm
10	M	45	50	280/180	0	0	0	+	++++	500	2.0	+	+	mod.	mod.	Acute pancreatitis
11	M	47	50	200/120	0	0	0	0	+	500	1.3	0	+	mod.	mod.	Ca. colon
12	M	49	52	220/140	0	+	0	0	?	580	2.0	+	+	min.	min.	Hemorrhage, peritoneal
13	M	50	52	218/104	+	0	0	0	?	550	2.0	+	+	min.	min.	Bronchiectasis
14	F	49	53	180/110	0	0	0	0	?	460	2.2	+	+	mod.	mod.	Mesenteric thromb.
15	M	54	54	240/120	0	+	+	0	+	480	2.0	+	+	mod.	mod.	Aortic aneurysm
16	F	53	55	200/135	+	+	+	0	++	300	2.2	0	+	mod.	mod.	Ruptured aneurysm
17	F	46	56	220/100	0	0	0	0	+	320	2.0	0	+	adv.	adv.	Postop. pulm. edema
18	M	31	56	220/120	0	0	0	+	?	470	2.0	+	+	adv.	mod.	Ruptured aneurysm

TABLE III

	Series I	Series II
Number in series:	44	18
Male:	26	9
Female:	18	9
Mean age at death:	70.8 years	50.0 years
Mean duration of known hypertension:	4.6 years	5.9 years
Heart:		
Mean weight:	430 gm.	443 gm.
S. D. heart weight:	113 gm.	109 gm.
Mean thickness, left ventricle:	1.76 cm.	1.90 cm.
Mean systolic B.P.:	204 mm. Hg	217 mm. Hg
Mean diastolic B.P.:	115 mm. Hg	126 mm. Hg
Headache:	18%	44%
Moderate or advanced renal arteriolosclerosis:	31.8%	72.2%

have existed for a long period of time. Furthermore, an examination of consecutive autopsy records of 70 patients who died after the age of 60, none of whom had a blood pressure previously recorded above 140 mm. Hg systolic and 90 mm. diastolic, disclosed 25.7 per cent with moderate or advanced renal arteriolosclerosis. This percentage, not too dissimilar from that of Bell [8] in normotensive patients, indicates that the incidence and degree of renal vascular damage in the older group of hypertensives approximates that found among older controls, and therefore cannot be attributed alone to the elevated blood pressure.

The group of younger, established hypertensives who died from some cause other than the usual complications is small, since patients fitting into this category were difficult to find. Nevertheless, only one subject of the 18 studied showed no vascular changes in the kidney, as compared to 11 (27 per cent) in the older age group.

In addition to the contrasting findings noted in the kidney, other small differences are evident in the study of the two series. Although the average heart weight was very slightly greater in the younger group, obviously no significance can be attached to this small difference. That the hearts weighed almost the same in both groups may have another explanation than the existence of hypertension. Nine of the subjects of the older group showed no coronary arteriosclerosis. The average heart weight for these nine patients (402 gm.) was less than that for the series as a whole. Thus coronary artery disease may have played an important part in the genesis of the cardiac hypertrophy seen in the older group.

The greater incidence and degree of renal arteriolosclerosis in the younger group of hypertensives, and the known high frequency of this pathologic change in patients with hypertensive vascular disease, afford but two alternatives. Either many of the patients in the older series had an unusually mild form of essential hypertension appearing late in life, or their hyper-

tension reflected an unrelated vascular degenerative process. It might be argued that all members of the older group represented patients with long-standing mild hypertensive vascular disease of a nonprogressive variety. However, three of these cases at least were known to be normotensive up to their sixth decade.

The following observations support the fact that many of the elderly hypertensives do not have hypertensive vascular disease in the usual sense. The incidence of renal arteriolosclerosis among the older hypertensives was but slightly greater than that found among normotensives of the same age, despite the fact that the severity of the pathologic changes in the older group was influenced by the unavoidable inclusion of patients with obvious essential hypertension. Although a comparable degree of cardiac hypertrophy was disclosed in both groups studied, the higher incidence of coronary arteriosclerosis in the older patients may have obscured a significant difference in heart weight. The difference in the sex incidence, frequency of headaches and degree of change on funduscopic examination are in keeping with this view.

This study does not eliminate the possibility that the elderly subjects may have a mild form of hypertensive vascular disease. The weight of evidence, however, supports the concept that many of the patients do not have this disorder. Although all patients in the older group showed a considerable degree of arteriosclerosis of the aorta, which could account for the systolic hypertension, no explanation has been offered for the elevation of diastolic pressure. It is conspicuous that the average age at death of these patients is 70.8 years, indicating that their hypertension is compatible with approximately a normal life span.

The possibility that individuals in later life may develop a hypertension of significant proportions on some basis other than that producing hypertensive vascular disease in younger persons should be considered in any study of the natural history of this disorder or in the practical management of patients.

Conclusions

1. A group of patients who died after the age of 60, with hypertension not known before the age of 55, was compared with another group of younger established hypertensives who died from some cause other than the usual complications of hypertensive vascular disease.

2. The incidence and degree of renal arteriosclerosis were considerably greater among the younger patients, while among the older patients they approximated those observed in elderly subjects with a normal blood pressure.

3. Although a mild form of essential hypertension cannot be excluded in this group of elderly patients, it is suggested that many instances of hypertension in later life may be due to some basis other than that producing the usual picture of hypertensive vascular disease.

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CASE REPORTS

MALIGNANT TUMOR OF THE THYMUS GLAND, MYASTHENIA GRAVIS DEVELOPING AFTER REMOVAL *

By JOHN B. FERSHTAND, M.D., F.A.C.P., *Fort Worth, Texas,* and ROBERT R. SHAW, M.D., *Dallas, Texas*

INTEREST in tumors of the thymus gland has been stimulated by their association with myasthenia gravis. Blalock,[1, 2] Clagett [3, 4] and others have reported on the sometimes apparently beneficial results of thymectomy in this disease. This case is unique in that symptoms of myasthenia gravis developed for the first time after subtotal removal of a malignant thymic tumor. We have been unable to find any reports of a similar occurrence in the literature. The duration of the known existence of this tumor, its great size, length of life after the appearance of symptoms, and the magnitude of involvement of the cardiac musculature are also unusual.

CASE REPORT

The patient was a white male, 27 years of age, who was first seen by us on February 20, 1947. He complained of generalized chest pain aggravated by an erect position, swelling of the veins of his neck and some difficulty in breathing. These symptoms had been present about three weeks and had been increasing in severity. He gave a history of having been told that he had had cardiac enlargement for some 10 years. He had been refused a commission in the Army after graduation from a military school because of this enlargement and had also been refused a commission at the beginning of World War II for the same reason. However, he had never had any previous cardiovascular symptoms and had always been an unusually active individual. He was able to do, without difficulty, all the vigorous work which his profession as a construction engineer required.

Our initial physical examination revealed evidence of caval obstruction with tremendous dilatation of the jugular veins, cyanosis of the face and upper extremities, and considerable telangiectasis about both costal margins. The area of cardiac dullness was greatly increased to both right and left of the sternum. Heart sounds were not remarkable and an electrocardiogram was normal. A roentgenogram of the chest revealed a mass extending along the right border of the heart shadow, continuous with the heart shadow, with what appeared to be a calcified border (figure 1). An oblique view further confirmed the impression that this was a tumor mass with a partially calcified capsule. He was admitted to the Baylor Hospital, Dallas, Texas, March 2, 1947, for surgical removal of the tumor in the right chest.

Operation: The right chest was opened through a posterolateral incision after removing a long length of the fifth rib subperiosteally. The pleural space was free of adhesions. A firm tumor with a calcified surface lay in the anterior mediastinum. The mediastinal pleura surrounding the tumor was incised and the adhesions binding the tumor to the adjacent structures in the mediastinum were separated both by blunt

* Received for publication March 19, 1949.
From the Harris Hospital, Fort Worth, Texas, and the Baylor Hospital, Dallas, Texas.

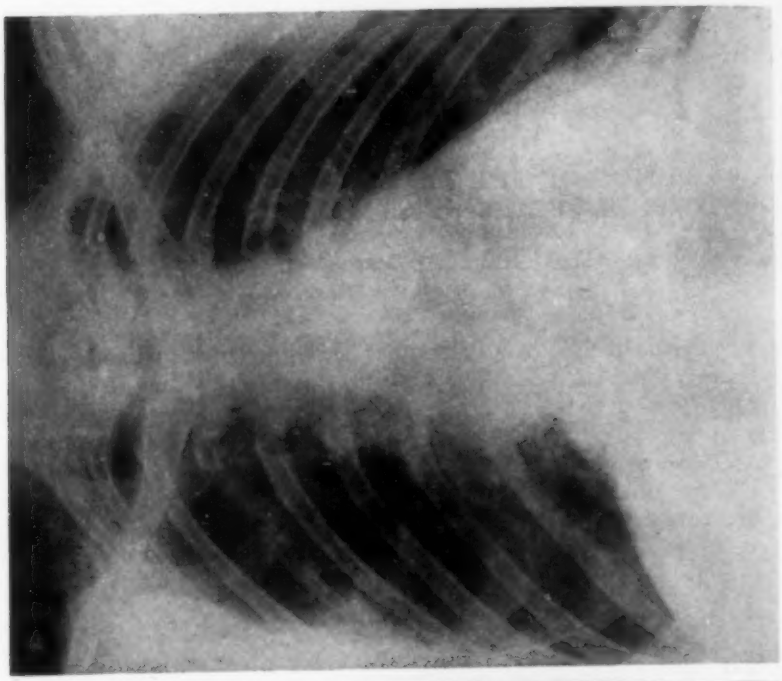

Fig. 2.

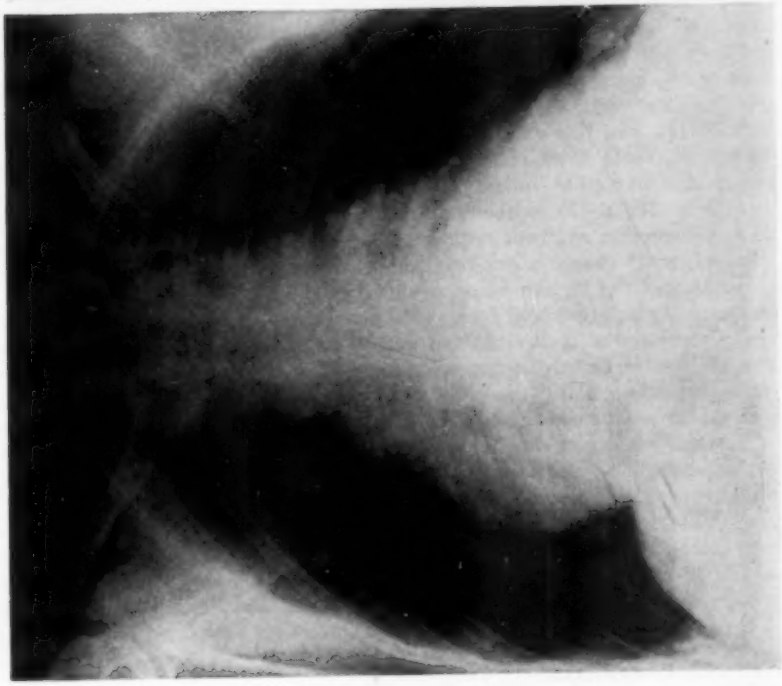

Fig. 1.

FIG. 1. Chest x-ray February 20, 1947. Tumor extending into the right chest, continuous with the heart shadow.
FIG. 2. Chest x-ray November 1, 1947. Heart shows very straight left border. Hilar glands on the right are moderately enlarged.

dissection and by ligation of the more vascular structures. The pedicle of the tumor was, at its upper pole, connected with the anterior mediastinum. It was secured with a ligature of no. 12 crochet cotton. One small section of the tumor wall, which was densely adherent to the structures in the anterior mediastinum, was cut across and removed following the freeing of the main tumor mass. After the large tumor had been removed from the chest an infiltration of cellular tissue approximately 2 cm. thick could be palpated in the anterior mediastinum. No attempt was made to resect this tumor mass since it was insinuated around the major vessels at the root of the heart. The lung was reëxpanded and the chest was closed with water-seal drainage. During the course of the operation the patient's condition was very unsatisfactory. The blood pressure would suddenly fall and seem to be unaffected by the administration of intravenous fluids. It was found that by lifting the weight of the tumor from the mediastinal structures his condition would improve. One ampule of cedilanid was given intravenously to support heart action. In spite of the fluctuating condition of the patient during surgery, his condition at the conclusion of the operation seemed satisfactory.

Postoperative Course: During the first two days the postoperative course was extremely bad. The nail beds were cyanotic and the patient complained of considerable difficulty in breathing and of dysphagia. The pulse was very irregular at times. He seemed to be in a prostrated condition, the exact cause of which could not be determined. On the second postoperative day the report was received from the department of pathology that the tumor removed was a malignant thymoma. In the face of this report it was felt that the profound prostration might be due to myasthenia gravis. Accordingly 1 c.c. of prostigmine 1 to 2,000 was given intramuscularly. Within a few minutes breathing became so much easier that oxygen could be discontinued, and his complaints of weakness and dysphagia disappeared. From that time on, prostigmine, 1 c.c. of 1 to 2,000, was given every six hours. During the remainder of the hospital course his improvement was rapid. The evidence of caval obstruction disappeared on the right, but it was found that the veins were still dilated on the left. Palpation of the left axillary vein revealed a phlebothrombosis. Dicumarol therapy was then started and the dosage continued, being carefully checked by prothrombin determinations. No emboli occurred and gradually the venous distention on the left receded.

Roentgen-ray therapy was started on the third postoperative day over the anterior mediastinum, as it was considered that the tumor was probably radiosensitive. A total dosage of 7,100 roentgen units was given over three ports to the anterior mediastinum. The patient was discharged from the hospital on March 19, 1947, on the eighteenth postoperative day.

The preoperative diagnosis was dermoid tumor of the anterior mediastinum, since the tumor was known to have been present at least 10 years, had been nonsymptom-producing, and had its position in the anterior mediastinum. The tumor also had a distinctly calcified capsule which lent further weight to this diagnosis. It was thought that the rapid onset of the signs of caval obstruction and difficulty in breathing was undoubtedly due to malignant changes in an anterior mediastinal dermoid tumor. At no time prior to surgery had there been any evidence or symptoms of myasthenia gravis.

In the early part of May the patient returned to work and complained only of some pain in his left chest aggravated by breathing. He was at that time taking one-half of a 15 mg. tablet of prostigmine three times a day. In August, 1947, he contracted a cold, complained of a constant dry cough, and began to have a daily temperature rise to around 100° F. This fever persisted almost continuously until the time of his death over a year later. A tachycardia with a rate of 102 was also

Fig. 1. Heart shows very straight left border. Hilar glands on the right are moderately enlarged.

noted at this time. His myasthenia was then apparently in an almost complete remission, and the prostigmine was discontinued entirely.

He continued working part time until October, 1947, when because of his difficulty in breathing, prostigmine was again resumed; on six 15 mg. tablets daily he noticed a definite improvement in his strength and endurance. He was advised to adjust the prostigmine to his own needs. On November 11, 1947, he reported that he had increased the dosage to eight tablets daily and had been feeling well until the preceding day, when he had experienced a severe upper right quadrant pain which had awakened him from sleep and had persisted since then. He was exquisitely tender over the liver and, in spite of failure to find cysts or trophozoites, a tentative diagnosis of amebic hepatitis was made and he was started on a course of emetine hydrochloride. There was immediate improvement, liver tenderness receded, temperature decreased and bowel movements which had been constipated became regular for the first time in many months. He was given a total of 6 gr. of emetine hydrochloride, 1 gr. daily.

During the next two months the liver tenderness reappeared and disappeared and was accompanied by pain in the left shoulder. A chest roentgenogram on November 1, 1947 (figure 2), showed nothing remarkable. The patient continued to have a low-grade fever and tachycardia and on January 6, 1948, was rehospitalized after a small hemoptysis. Another chest roentgenogram was identical with that taken November 1, 1947. With bed rest and penicillin his temperature returned to normal and his heart rate dropped from 120 to an average of 102 to 104. An electrocardiogram taken at this time showed inversion of $T_{1, 2 \text{ and } 3}$ which had not been present in his original electrocardiogram taken in March, 1947, just prior to his surgery. Shortly after discharge from the hospital he again began to have fever and pain, and tenderness in the right costal margin again appeared. He was sent to the Mayo Clinic for study. The day after his arrival in Rochester he had an acute attack of paroxysmal arrhythmia which proved to be an auricular flutter (figure 3) with 2 to 1 block. Sinus rhythm returned after medication with digitalis and quinidine. He was given further roentgen-ray therapy in the region of the tumor and on his return home his pulse rate was 96. No evidence of myasthenia gravis was present and he had again discontinued the use of prostigmine.

From January until May of 1948, he was forced to spend most of his time in bed; the tachycardia continued with a rate averaging 110 to 120, occasionally after slight exertion increasing to 140 to 160. He also continued to have a daily rise in temperature from 99.5 to 100.5° F. From March 1 to 6, he was given roentgen-ray therapy over the right lower chest wall because of pain and swelling in this region, an additional 1,800 roentgen units. He complained of weakness on May 12, 1948, and prostigmine, three 15 mg. tablets a day, was again resumed with subjective improvement. On May 18, 1948, he developed a paroxysmal arrhythmia which lasted about 30 minutes and subsided before he could be seen, and again that afternoon he had a similar attack lasting only about five minutes. A tracing (figure 4) taken between these attacks showed no conduction defects or arrhythmias. On May 20, his temperature rose to 102° F. and was accompanied by a progressively severe dyspnea; he became quite cyanotic and the neck veins became markedly distended. On examination there was dullness over the lower left hilar region with accompanying moist râles, and a diagnosis of bronchopneumonia of the left base was made. This was confirmed by roentgenogram, which also showed an increase in the size of the heart shadow. He was placed in an oxygen tent, and treatment with penicillin, 50,000 units every three hours, was started. This resulted in an almost immediate drop in temperature to a normal level, where it remained until shortly before he died.

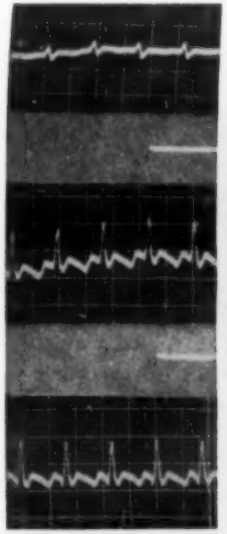

Fig. 3.

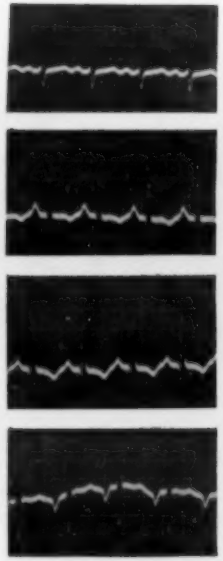

Fig. 4.

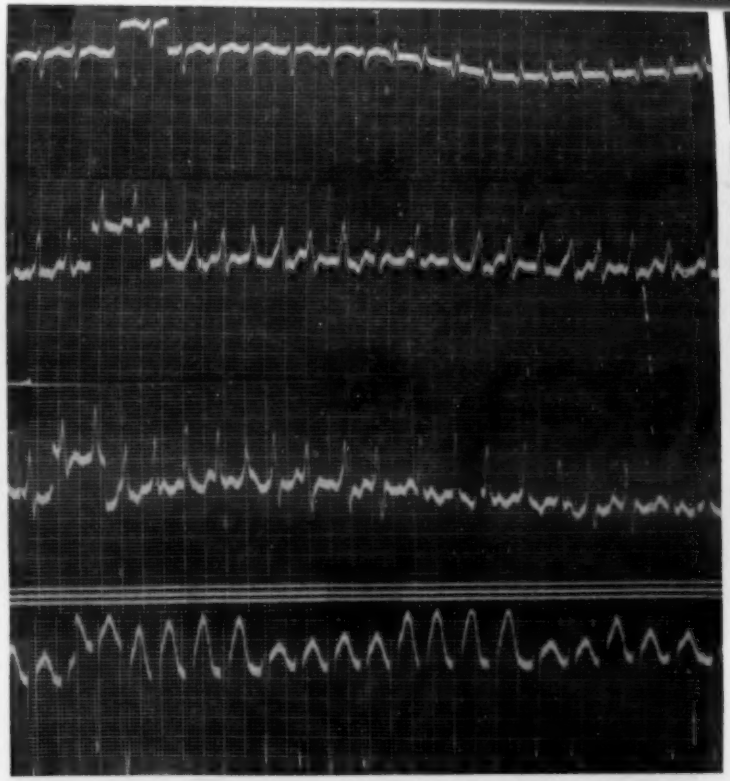

Fig. 5.

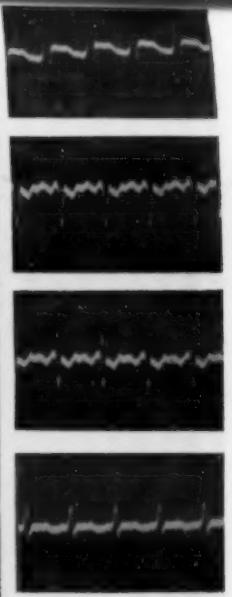

Fig. 6.

FIG. 3. Electrocardiogram January 31, 1948. Auricular rate 350, ventricular rate 75. Auricular flutter with 2:1 block.

FIG. 4. Electrocardiogram May 18, 1948. Auricular rate 120, ventricular rate 120, sinus tachycardia. Right axis deviation. $T_{2 \text{ and } 3}$ inverted. R in lead CF is very tiny and T flattened.

FIG. 5. Electrocardiogram May 25, 1948. No definite P waves are discernible; ventricular rhythm is totally irregular; rate averages 220 per minute. There is great variation in the configuration of the ventricular complexes, and the IV conduction time varies from .06 to .14 of a second. Probably auricular fibrillation with paroxysmal bundle branch block.

FIG. 6. Electrocardiogram May 26, 1948. Auricular rate 300, ventricular rate 150. Auricular flutter with 2:1 block.

Some improvement occurred in the next five days, but on May 25 he again developed a paroxysmal arrhythmia with an irregular ventricular rate of around 220. An electrocardiogram (figure 5) was obtained, and because of its bizarre appearance we now felt certain that there was a definite tumor invasion of the heart muscles. He was given 1.2 mg. of digitoxin intravenously, and after 36 hours the cardiac rate suddenly decreased to 130 and another electrocardiogram (figure 6) showed an auricular flutter with a 2:1 block. In a last effort to stem the course of the disease, another course of roentgen-ray treatment directed to the heart was started on June

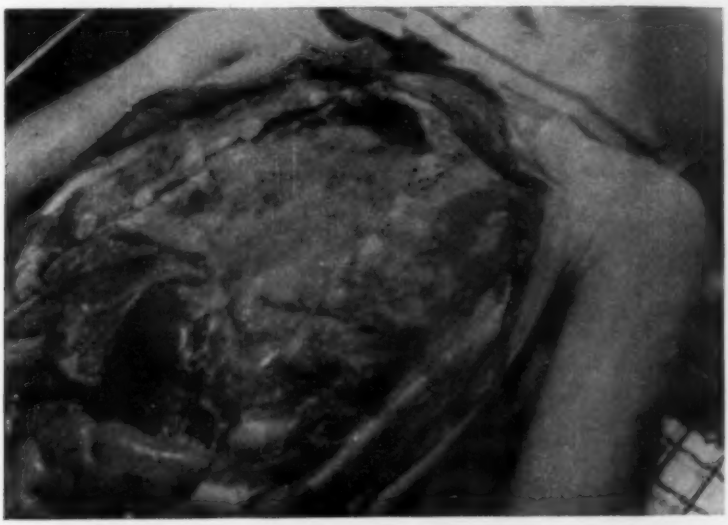

Fig. 7.

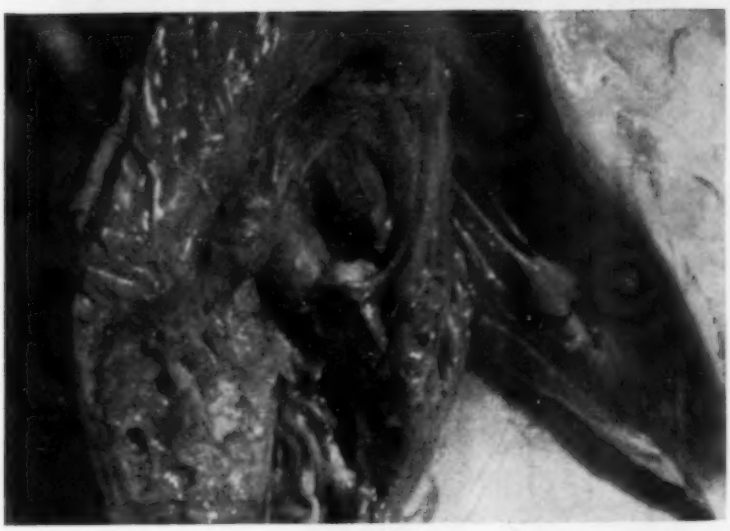

Fig. 8.

FIG. 7. Breast plate removed, showing replacement of the pericardium by tumor tissue.
FIG. 8. Tumor tissue invasion of the wall of the right ventricle. Pedunculated tumors are seen to lie in the cavity of the ventricle.

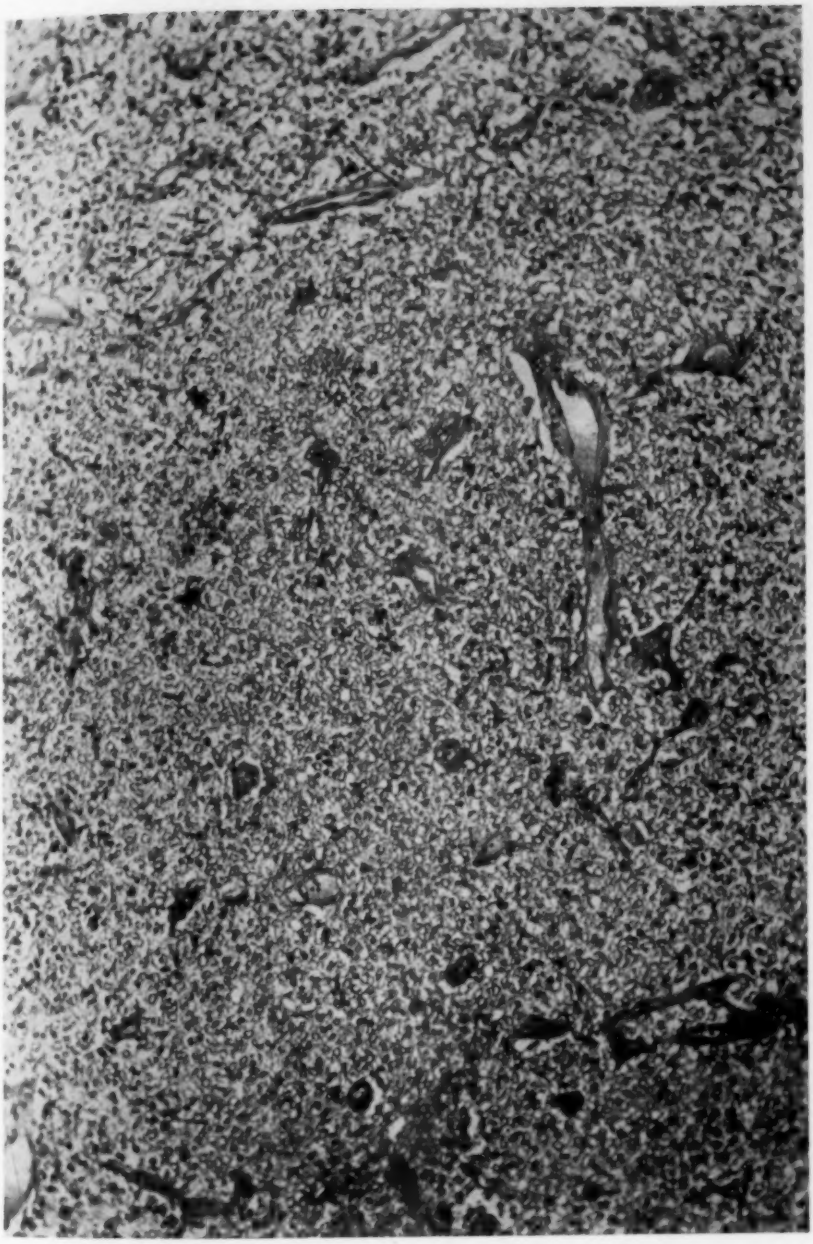

FIG. 9. Photomicrograph. Section of tumor removed at the time of surgery. Cells are predominantly small round cells with dark staining nuclei and scanty cytoplasm. Diagnosis, sarcoma of thymus.

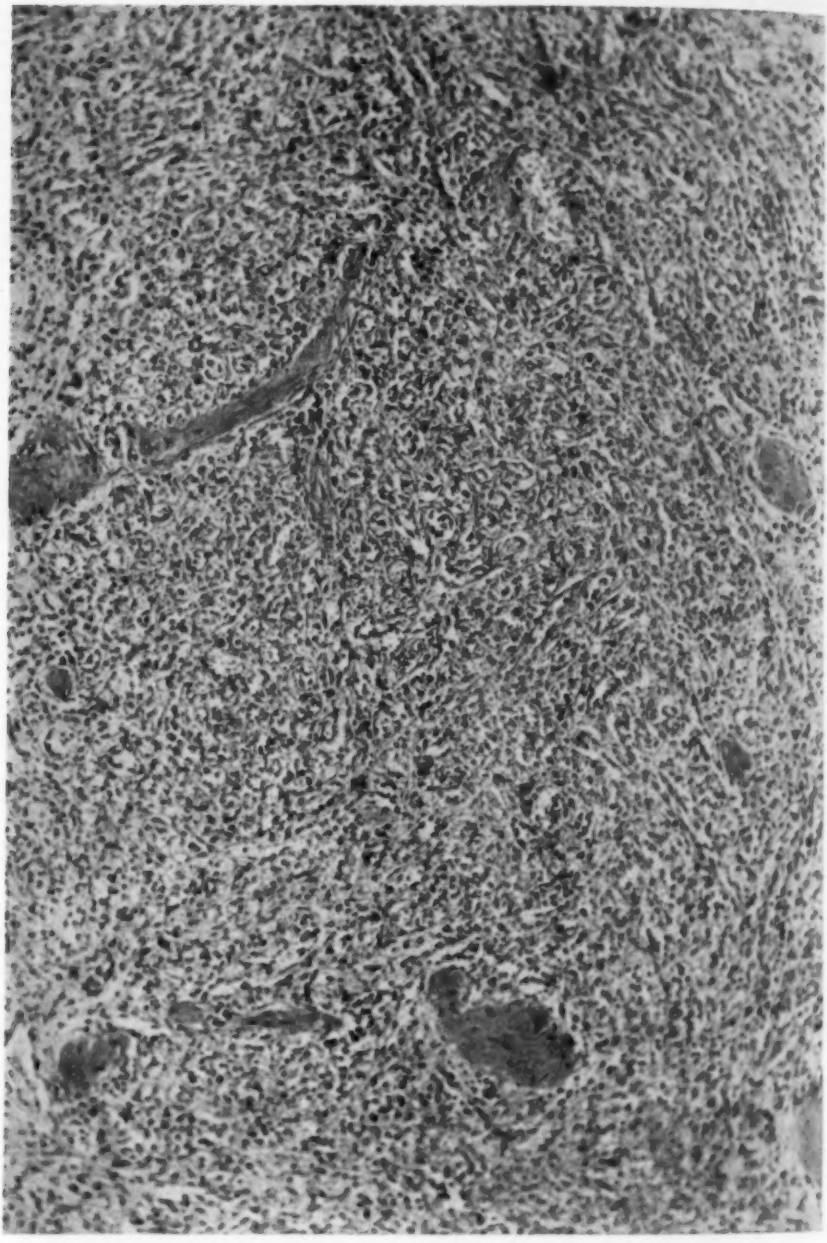

FIG. 10. Photomicrograph. Section of tumor invading myocardium. A few tiny bundles of muscle are seen. The predominating histology is identical with that of the original tumor.

3. There was some decrease in the size of the neck veins in the following week. On June 10 he had a great deal of respiratory difficulty, unrelieved by prostigmine, 15 mg. every two hours orally, and only partially relieved by parenteral prostigmine, 1–2,000. His respiratory difficulty increased in severity, and on June 11 he was placed in a respirator and given nasal oxygen. There was very little change in his condition until June 19, when signs of circulatory failure appeared, pulse became extremely rapid and thready, blood pressure was unobtainable, and his temperature began to rise and, on June 21, had reached a level of 106° F. He was at this time comatose and died at 6:25 p.m.

Autopsy: The autopsy was performed three hours after death.

On removal of the sternal plate a sheet of pearly white tissue was encountered (figure 7). The pericardial sac was obliterated and this firm neoplastic tissue had apparently replaced the pericardium and infiltrated into and through the myocardium, forming papillary projections in the right ventricular cavity measuring 2 by 1.5 cm. (figure 8). The heart, together with the neoplastic tissue, weighed 990 gm. There was infiltration of the neoplastic tissue into the right diaphragm. Several caseous areas were noted along the base of the lungs on the diaphragm which appeared to be extension of the neoplastic tissue which had undergone caseation. The largest of these areas was 2 cm. in diameter. There was no extension or metastasis to any of the abdominal viscera.

Sections through the pericardium, epicardium, myocardium and endocardium revealed a most extensive replacement of the myocardium by either actual malignant tissue or by necrosed areas of the infiltrating tissue. It was obvious that there had been impairment of circulation, since the myocardial fibers themselves, where present, were poorly formed and poorly nourished. The pattern suggested a most universal and extensive involvement. It appeared, however, to be of neoplastic type, with the thymoma cells occluding and obstructing the arterial circulation through the myocardial fibers themselves. The polypoid masses in the right ventricle were made up almost entirely of necrotic tissue and malignant forms. The cell type was largely small round cells, with very prominent dark staining nuclei and scanty cytoplasm. The nucleoli were not well formed. There was no reproduction of elements suggesting the epithelial portions of the thymus. No Hassall's corpuscles were observed.

Numerous sections were made through the cardiac structures, and the pathologist estimated that three-fourths to four-fifths of the heart had been replaced by neoplastic tissue. Sections of the original tumor (figure 9) and those obtained from the heart at autopsy (figure 10) show identical histologic patterns.

Discussion

Malignant tumors of the thymus gland may arise from the lymphoid or epithelial systems of the thymus. The thymus may also be involved in generalized diseases such as Hodgkin's and leukemia, and the so-called leukosarcoma of Sternberg may be another separate entity in which the thymus is implicated. Symmers [5] and Wilson and Pritchard [6] found similar incidences of .014 per cent in their reports of series gathered from autopsy material. These authors offer pathological classifications of these tumors; all found definite differences in extension and metastasis in the different classifications.

In Symmers' series of 25 cases, six could be classified as lymphosarcoma, and in five of these the heart muscles were invaded; the pericardium was invaded in all six. In one case of Hodgkin's disease in this series, the muscle tissue of the auricles and the upper one-third of the right ventricle were almost completely replaced by tumor tissue. In Wilson and Pritchard's series of 11 cases, similar invasion of the pericardium and myocardium was found in the lymphosarcomas.

Harrell,[7] Ritvo [8] and McCoy [9] have reported on the massive invasion of the cardiac structures occasionally encountered in Hodgkin's disease.

Wilson and Pritchard [6] present an excellent description of the lymphatic drainage of the thymic region. They point out that tumors derived from the epithelial structures of the thymus almost invariably show lymphatic metastasis with extension into the superficial and deep cervical lymphatic and into the anterior mediastinal glands, then to the tracheobronchial glands. In the last instance, the presenting picture is often similar to that of a bronchogenic carcinoma. The perirenal glands, pancreas and adrenals may also be involved.

Leukosarcoma was first described by Sternberg in 1908. The picture is that of enlarged thymus, liver, spleen and lymph glands, with a terminal blood picture of a lymphatic leukemia. The first symptom in these patients usually is edema of the face produced by obstruction from the tumors, and a rapidly fatal course ensues. All of these tumors show a marked predilection for the male sex. As in our case, the earliest symptoms are usually those due to pressure on the anterior and superior mediastinal structures. Death commonly ensues in a matter of days or weeks after the first symptoms. One of Symmers' cases lived for a period of 13 months, the remainder died in from four to 120 days. Our patient's survival period of 18 months is, therefore, remarkably long. Clagett [4] reports that 11 of his patients had roentgen therapy before, after, or before and after surgery. He is not specific as to the type of tumors encountered in these patients, but states: "It is of interest to note that those patients in whom some tumor tissue was removed and who received roentgen therapy are alive and getting along surprisingly well even in the presence of what appeared at operation to be an invasive malignant lesion." However, these were individuals who had had partial thymectomies for myasthenia gravis and in whom the invasion of the tumor had not progressed to the point of producing symptoms of mediastinal obstruction.

With the present state of our knowledge, early radical removal of these tumors with resultant cure is almost impossible because of the extreme difficulty in making an early diagnosis. Symptoms of myasthenia gravis warrant a thorough search for thymic tumor. Good [10] reviewed the roentgenograms in 100 cases in which the thymus was removed because of myasthenia gravis. In only 17 out of these 100 cases was a mass seen in the roentgen-ray films. In only seven of these was there a well defined mass, and in only two was there any deposit of calcium. He believes that roentgenoscopy is of the greatest value and is superior to roentgen-ray films in studying patients with possible thymic tumors.

Summary

A case of malignant tumor of the thymus gland has been presented. This patient showed the usual involvement of the cardiac structures previously reported in sarcomas arising from this gland.

The occurrence of the first symptoms of myasthenia gravis postoperatively, the massive involvement of the cardiac musculature, and the length of survival after appearance of symptoms are unique.

The necessity for removing symptomless intrathoracic tumors is further emphasized by the fatal outcome in this case. We may surmise that the large amount of roentgen-ray therapy this patient received contributed to his partial recovery and materially prolonged his life.

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FATAL AGRANULOCYTOSIS DURING TREATMENT OF TOXIC GOITER WITH PROPYLTHIOURACIL *

By Richard T. Beebe, M.D., F.A.C.P., Simon Propp, M.D., John C. McClintock, M.D., and Armand Versaci, M.D., *Albany, New York*

The introduction of antithyroid drugs as therapeutic agents for the treatment of toxic goiter led to the belief that surgery would no longer be necessary to relieve hyperthyroidism. The accumulated experience of the past seven years has failed to support initial hopes and, in addition, has indicated certain hazards associated with the use of these drugs. Although new and less toxic forms of the original antithyroid agent have been developed, they cannot be used indiscriminately.

A few carefully selected patients can obtain a cure of their hyperthyroidism from the judicious use of antithyroid agents alone. Many patients undergo thyroidectomy with increased safety because of pre-operative preparation with these drugs. A small number of patients who need but refuse operation can have their thyrotoxicosis controlled by medical means. Whether antithyroid drugs are used as the sole therapeutic agent, as an adjunct to surgery or in a palliative manner, the doctor must keep the patient under close observation for possible toxic effects.

Thiouracil, the first of these compounds to be widely used, has now been almost completely replaced by the propyl form. Toxic reactions occurred in about 13 per cent of all cases receiving thiouracil,[16] with a mortality of 0.5 per cent, due to agranulocytosis.[11] To avoid these unpleasant and fatal complications, many other compounds [1] have been tested for widespread clinical use, and all except

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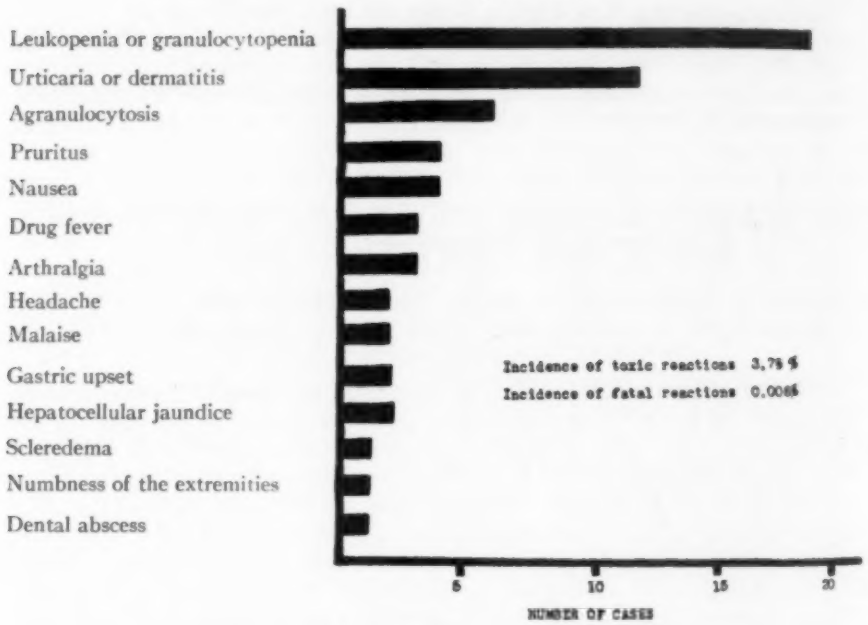
From the Departments of Medicine and Surgery, Albany Medical College and the Albany Hospital.

propylthiouracil have been rejected. This compound is as effective in the treatment of hyperthyroidism as thiouracil, and has the advantage of being much less toxic. Unpleasant and even dangerous toxic manifestations are caused by propylthiouracil in 2 to 4 per cent of the cases receiving the drug. The reactions observed are similar to those produced by thiouracil.

The toxic reactions most frequently reported, leukopenia with or without granulocytopenia, occurred in 19 of 1,651 patients treated with propylthiouracil.* The case being reported is one of the first fatalities attributed to agranulocytosis caused by the use of this medication. Four nonfatal cases of agranulocytosis due to propylthiouracil and one death are recorded in the literature.[3, 10, 19] Toxic

TABLE I

62 Toxic Reactions in 1651 Reported Cases
Treated with Propylthiouracil



effects of propylthiouracil include 12 cases of dermatitis and urticaria. Pruritus, nausea, drug fever, arthralgia, headache, malaise and gastrointestinal disturbances are reactions observed less frequently. The accompanying table lists additional complaints that have been considered to be due to the use of antithyroid medication.

Obviously the most serious complication is agranulocytosis, with its antecedent leukopenia and granulocytopenia. What precautions are required to detect the onset of these toxic reactions? One authority [5] states that the white blood cell and differential counts should be obtained one week after starting treatment and every three months thereafter. A common practice is to obtain blood counts

* Table 1 compiled from references 2, 4, 6, 7, 8, 9, 10, 12, 13, 14, 15, 17 and 18.

only if toxic symptoms appear. This method requires a close patient-doctor relationship to prevent delay in detecting the onset of toxic symptoms. Only those patients who are alert, intelligent and coöperative should be permitted to use antithyroid drugs to control, or to attempt medical cure of, toxic diffuse goiters. A total white cell count under 4,000, or a reduction of the segmented granulocytes below 40 per cent, are indications to stop the use of propylthiouracil. Careful, frequent examination of the blood is then essential until the white cell count is reestablished in a safe range. The drug need not be discontinued for some of the other toxic reactions if very close supervision of the patient can be maintained.

Case Report

A widowed white female, aged 85, who lived alone, was seen as a private outpatient (J. C. M.) on July 20, 1948, with the chief complaints of weakness and tremors. These had been present for four months. Her symptoms were nervousness, irritability, fatigability, warm, trembling hands, choking spells, and ankle edema. She had experienced some diarrhea. Despite a good appetite, her weight had decreased from 138 to 96 pounds. The patient had taken digitalis for ankle edema for four months. She had known of her goiter for 39 years.

Examination revealed a well preserved elderly woman with an obvious goiter. Eye signs of hyperthyroidism were not present. The thyroid gland was greatly enlarged by multiple adenomas that extended substernally on both sides of the neck. The trachea was displaced posteriorly. The heart was enlarged but the sounds were

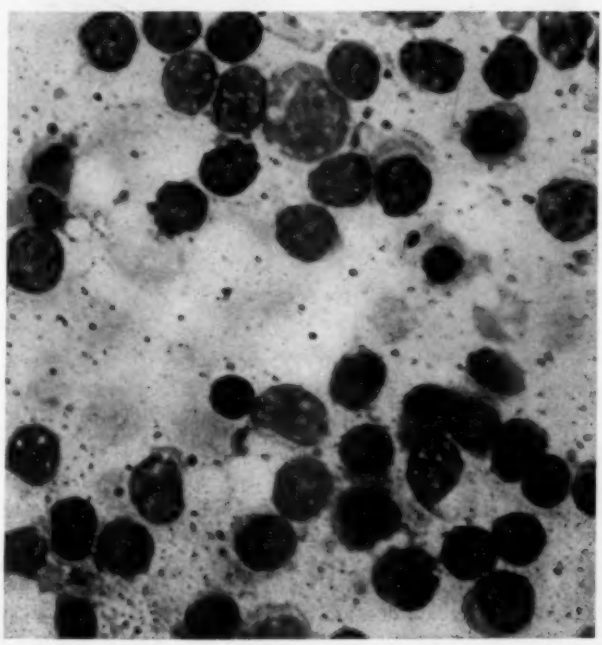


Fig. 1. Marrow smear prepared from sternal aspiration. Wright stain, × 850. Predominant cell is mature lymphocyte. A few large lymphocytes and metarubricytes (polychromatic normoblasts) are present. Striking feature is complete absence of granulocytes and their precursors.

of good quality. There was a systolic murmur at the apex. There were occasional premature beats. The blood pressure was 148 mm. mercury systolic and 80 mm. diastolic. The pulse rate was 96. There was pitting edema over the tibiae. Dilated superficial veins were present over the neck and upper chest. The clinical impression was toxic nodular goiter and associated aggravation of arteriosclerotic heart disease.

An initial dose of 100 mg. of propylthiouracil twice daily was prescribed, together with one capsule of multiple vitamins. Digitalis, which had previously been taken by the patient, was continued as purodigin, 0.2 mg. each day. The patient was observed two weeks later, at which time her weight was 95 pounds. The pulse rate was 104, and the blood pressure was 152 mm. mercury systolic and 70 mm. diastolic.

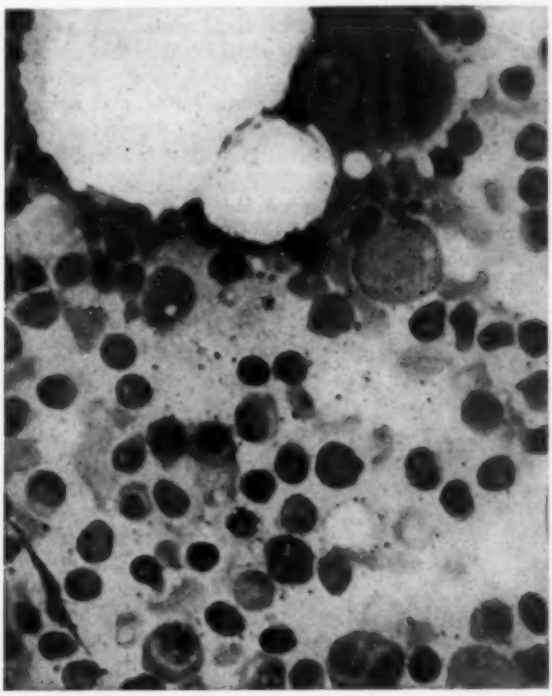


FIG. 2. Marrow smear prepared from sternal aspiration. Peroxidase-Wright's stain, × 550. There is complete absence of the oxidase-positive granulocytic cells. An immature megakaryocyte and a rubriblast (pronormoblast) are shown at top of figure. There is active erythropoiesis.

Slight subjective improvement had taken place, but because it was felt that an inadequate amount of the antithyroid drug had been prescribed the dose was increased to 250 mg. daily.

The patient was cautioned to report any sore throat, difficulty in swallowing, skin eruption or nausea. Reëxamination in three weeks revealed that her weight had dropped to 83.5 pounds and that she was obviously ill. There was a history of cough for one week prior to this visit. The patient was admitted to the Albany Hospital immediately.

Physical examination on admission, August 30: temperature 101, pulse 125, respirations 20, blood pressure 120 mm. mercury systolic and 70 mm. diastolic. The pertinent findings were the goiter, hot, dry skin, and coated tongue. The uvula was edematous and the pharynx was injected. The lungs were normal. The heart was enlarged, the rate rapid, and the rhythm regular. A rough apical systolic murmur was noted. Her abdomen was normal. There was no ankle edema.

Laboratory studies revealed a trace of albumin in the urine. Fasting blood sugar was 123 mg. per cent and nonprotein-nitrogen, 37 mg. per cent. The Wassermann test was negative. Slight cardiac enlargement was observed in the report of the chest roentgenogram. An electrocardiogram showed left axis deviation with evidence of myocardial damage, probably on an arteriosclerotic basis. Sinus arrhythmia was present.

The blood picture was the most important of the laboratory findings: hemoglobin 8.5 gm., red blood cells 2,300,000, and white blood cells 3,500. The differential count showed segmented neutrophils 26, lymphocytes 73, and monocytes 1 per cent. A differential count later the same day revealed 100 per cent lymphocytes. In spite of treatment during the first three hospital days, the white cell count fell to 1,150, all of which were of the lymphocytic series.

Sternal marrow aspiration two days after admission showed reduced cellularity, with a complete absence of the granulocytic series, including myeloblasts. Erythropoiesis was normoblastic and moderately decreased. Many mature lymphocytes were seen, and a few immature forms were present. Lymphocytes and plasma cells had replaced normal marrow elements to a marked degree. Megakaryocytes were present in normal numbers. The diagnosis was: advanced stage of agranulocytosis * (figures 1 and 2).

The following therapy was instituted: 300,000 units of penicillin G intramuscularly twice daily. Fluid intake was maintained to a minimum of 2,000 c.c. daily by intravenous administration of 5 per cent dextrose in distilled water. Multiple vitamins were continued. Blood transfusions of 500 c.c. each were given on three successive days. Purodigin was continued. Liver extract, 10 units intramuscularly, was given daily. Nasal oxygen was administered during the last 24 hours of life. In spite of these measures, the patient died five days after admission. Permission for postmortem examination was not granted.

Comment

It does not seem possible to draw up a dogmatic schedule to be followed by patients receiving propylthiouracil. Nevertheless, the curative, pre-operative and palliative use of this compound requires close supervision. Careful selection of patients, according to their ability to understand and to carry out directions, is essential. The frequency with which blood counts are taken remains on an empirical basis. Certainly bi-weekly white cell counts for eight weeks, followed by counts at four week intervals, would appear to be justified. Elderly patients may require more frequent observations than younger individuals. Any increase in dosage of propylthiouracil requires more frequent observations of the white cell count. Instructions to report toxic manifestations should be reëmphasized to the patient at each visit.

* This unusual marrow picture has been observed by one of us (S. P.) in another case of agranulocytosis, proved at autopsy, in which the complete absence of cells of the granulocytic series followed the administration of sulfonamide drugs.

SUMMARY

1. The toxic reactions associated with the use of antithyroid drugs are discussed.

2. Suggestions that may help to minimize the development of the more serious complications resulting from the use of propylthiouracil are presented.

3. The record of a patient who died from agranulocytosis while taking propylthiouracil is given.

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A REFRACTORY CASE OF IDIOPATHIC STEATORRHEA (NONTROPICAL SPRUE), WITH OBSERVATIONS ON THE THERAPEUTIC EFFECTS OF SALT-POOR HUMAN ALBUMIN AND OF THE ADRENOCORTICOTROPIC HORMONE *

By THOMAS P. ALMY, M.D., *New York, N. Y.*

TREATMENT of cases of tropical sprue by means of diet, vitamin supplements, and liver extract, folic acid, or vitamin B_{12} is considered to be satisfactory in the great majority of cases. In the closely related syndrome of idiopathic steatorrhea (nontropical sprue), these measures are often inadequate to bring on a remission, and occasionally a patient with this disorder will become progressively worse despite well-directed and intensive therapy. In such a resistant case, we have been led to administer concentrated human albumin, and subsequently ACTH, with favorable results. This report is concerned with the description of these therapeutic effects, and with a discussion of their mechanisms and potential significance.

CASE REPORT

A 44 year old white housewife was uneventfully delivered of her third child in 1939. She immediately developed a diarrhea of two to four large, liquid, foamy, pale, foul-smelling stools per day, lasting six weeks. Four weeks later her infant son developed a similar diarrhea, which was promptly diagnosed as celiac disease and from which he slowly recovered after about two years. In the eight years after her first attack, the patient had similar diarrhea lasting one to three days and occurring on the average every three months.

In 1947 diarrhea reappeared in more severe form (four to 12 bowel movements per day), and has persisted with only short remissions until the present. She has had continued anorexia and abdominal distention, and occasional vomiting. In six months her weight fell from 62 to 48 kg., and she developed numerous bruises, gastrointestinal bleeding and manifest tetany. Although she sometimes had typical cheilosis, she never developed glossitis, aphthous stomatitis, pellagrous dermatitis or night blindness.

On admission, July 3, 1947, examination revealed a strikingly emaciated woman with gray hair and marked diffuse tanning of the skin. Blood pressure was 82 mm. Hg systolic and 40 mm. diastolic. The mucous membranes were free of inflammation, ulceration or abnormal pigmentation. The abdomen was protuberant and tympanitic; the liver and spleen were not felt. There was no enlargement of peripheral lymph nodes. The Chvostek and Trousseau signs were positive. Rarely, spontaneous carpopedal spasm was observed.

The hemoglobin value was 13 gm. per 100 c.c., the red blood cell count 4.4 million per cu. mm. At other times the hemoglobin has been as low as 7.5 gm., with 2.5 million red blood cells. Macrocytosis has never been observed. Initially, total serum proteins were 7.4 gm. per cent, with 3.5 gm. albumin and 3.9 gm. globulin. Serum calcium was 4.9 mg. and phosphorus 4.5. Both oral and intravenous glucose tolerance curves were flat. The plasma vitamin A level was 15.9 May units, and fell to 12.3 units five hours after oral ingestion of 420,000 units of vitamin A. Gastric analysis yielded a maximum of 100 units of free HCl after histamine. Secretin test revealed

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From the Department of Medicine, the New York Hospital-Cornell Medical Center.

TABLE I

Relationship of Serum Albumin to Clinical Condition of Patient

Date	Treatment	Total Serum Protein	Serum Albumin	Clinical State
8/6/49	—	5.1	2.9	Watery diarrhea, (6–7 x/day) anorexia, weakness, distention
8/24/49	Plasma; blood	6.7	3.6	1–2 formed stools per day, good appetite and strength
9/21/49	—	6.1	3.2	Diarrhea
10/21/49	—	5.4	2.1	Diarrhea, anorexia
11/7/49	Albumin	5.9	3.6	Constipated, good appetite
11/30/49	—	7.2	4.3	Diarrhea, anorexia
1/10/50	—	5.5	2.1	Diarrhea, weakness
1/23/50	Plasma; blood; albumin	6.7	4.3	1–2 stools/day; stronger
1/30/50	—	6.6	3.9	Diarrhea, weakness

normal values for volume, bicarbonate and enzyme content of the pancreatic juice. The stools were copious, liquid to soft, foamy and foul. Cultures and microscopic examinations disclosed no bacterial pathogens or animal parasites. Quantitative 24 hour collection was of large volume, with excessive fat content on chemical analysis. The colon was found to be normal on proctoscopy and barium enema, but small intestinal roentgenograms showed delayed and discontinuous propulsion, loss of delicate mucosal pattern, and clumping or "puddling" of the barium.

Treatment was begun with a high protein, high carbohydrate, low fat diet, supplemented by potent concentrates of multiple vitamins and by oral and parenteral B complex factors and parenteral vitamin K. To raise the serum calcium to normal,

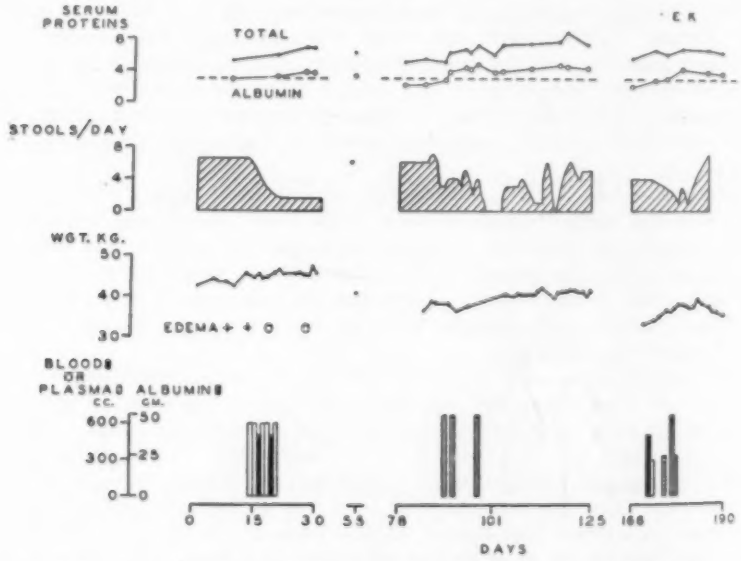

FIG. 1. Changes in diarrhea and in serum protein levels induced by three courses of treatment with plasma, blood and salt-poor human albumin. Broken line indicates lower limit of concentration of serum albumin in normal persons.

an initial daily oral dosage of 2,000,000 units of concentrated vitamin D in oil (400,000 units per c.c.) was needed, together with 4.8 gm. of powdered calcium lactate by mouth.

Since her discharge on September 13, 1947, 800,000 units of vitamin D per day have been required for maintenance. The adequacy and safety of this measure have been repeatedly checked by serum calcium determinations and at least weekly qualitative tests for urinary calcium (Sulkowitch reagent). The intramuscular injection of crude or refined liver extracts was without effect on the patient's weight, diarrhea or meteorism. Folic acid, 100 mg. per day by mouth, has been used in two long courses without benefit. Vitamin B_{12} has been given by muscle at two levels of dosage,

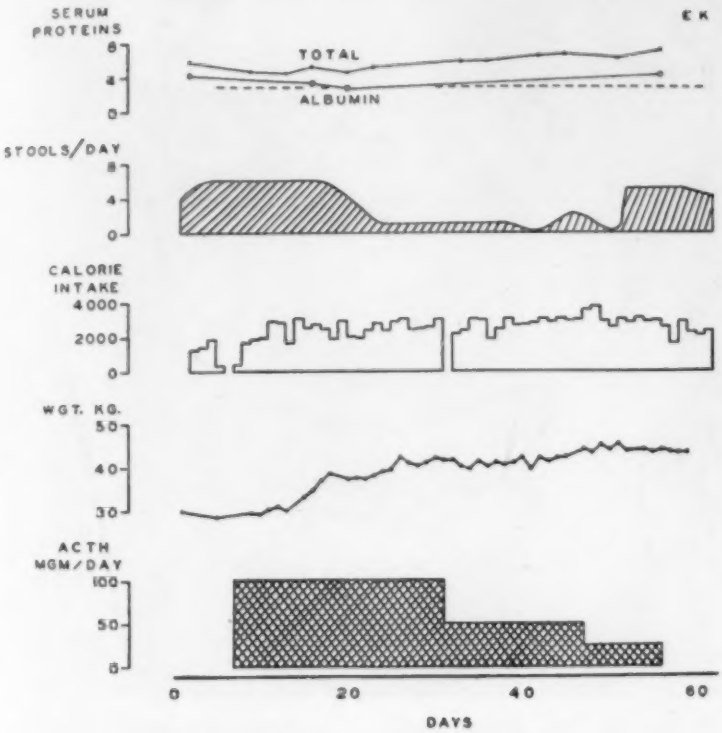

FIG. 2. Results of treatment with ACTH.

10 and 100 gamma per day, with no improvement. Prolonged and supposedly adequate treatment with pancreatin and with Tween 80 has been ineffective. Except for short periods of clinical improvement unrelated in time to the above therapeutic efforts, the condition of the patient has steadily deteriorated. Only the hypocalcemia has been steadily under control.

In July, 1949, during a period of increasing weakness, anorexia, watery diarrhea, edema and rapid weight loss, she was found to have a total serum protein of 5.1 gm., with an albumin level of 2.9 gm. (table 1, figure 1). After infusion of 8 units of plasma and transfusion of 1,000 c.c. whole blood in the course of six days, the serum proteins rose steadily to 6.7 gm. (albumin 3.6 gm.). Her weight remained the same, but edema disappeared. Her appetite and her strength rapidly increased; abdominal

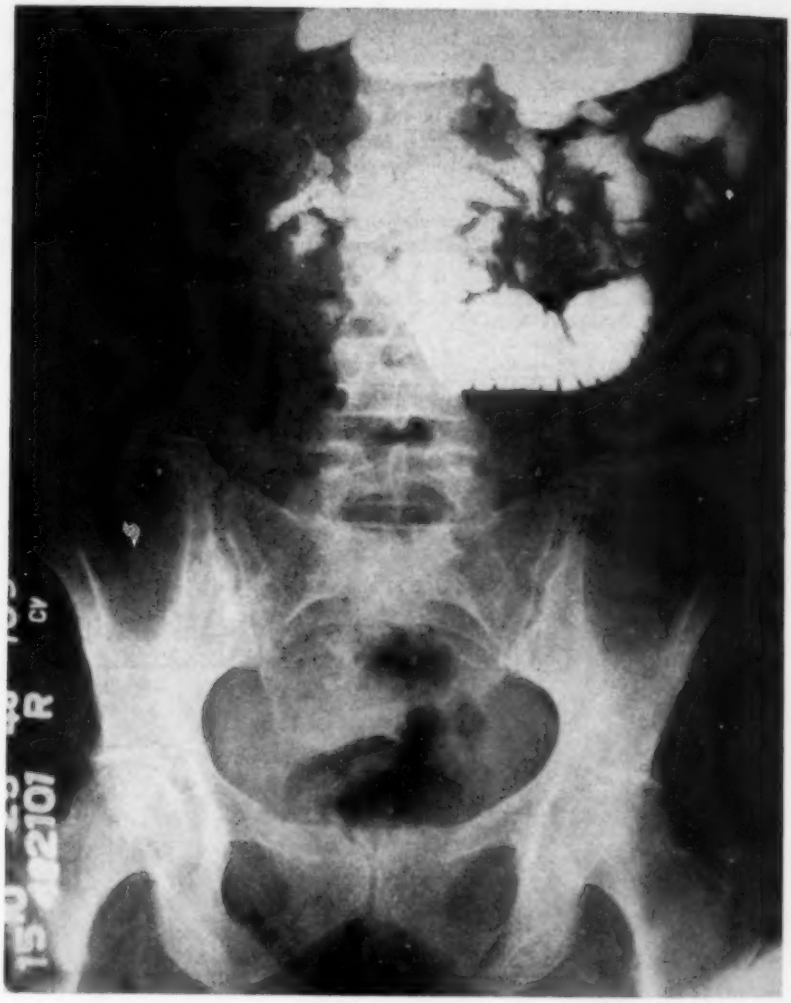

FIG. 3. October 25, 1948. Roentgenogram 15 minutes after barium by mouth, showing delayed motility and dilated, coarsened jejunal loops.

distention subsided; her diarrhea disappeared. Four weeks later, although the serum proteins were still normal (total 6.1, albumin 3.2), symptoms returned and her weight again fell. In the succeeding two weeks, despite the administration of 1,500 c.c. of pooled plasma, the serum albumin continued to fall. There was no clinical improvement. Between October 25 and November 2, 1949, 150 gm. of salt-poor human albumin * were given intravenously, raising the serum albumin level from 2.1 to 4.7 gm., and again inducing a remission of symptoms, which lasted for two weeks. Between January 14 and January 21, 1950, 500 c.c. of bank blood, 300 c.c. of pooled plasma and 100 gm. of salt-poor albumin were administered, with rise of serum albumin from 2.1 to 4.3 gm., and with remission of symptoms for only one week.

* Supplied through the courtesy of the American Red Cross National Blood Program.

Between February 9 and 16, six 25 gm. units of human albumin were given. The serum albumin level was normal at the start, and unchanged by this course of treatment. There was no reduction in watery diarrhea, anorexia or distention. The data indicated that whenever clinical improvement was obtained with plasma or salt-poor albumin, it coincided with a rapid rise of the serum albumin from a subnormal to a normal level.

In May and June the patient rapidly lost further ground, with continued severe watery diarrhea, anorexia and distention. Her weight fell to 28.8 kg., and her appearance was one of extraordinary emaciation. She was unable to rise from her bed without assistance. Her skin was cold, her mucous membranes were parched and her peripheral veins collapsed. On June 10 intramuscular injections of sterile

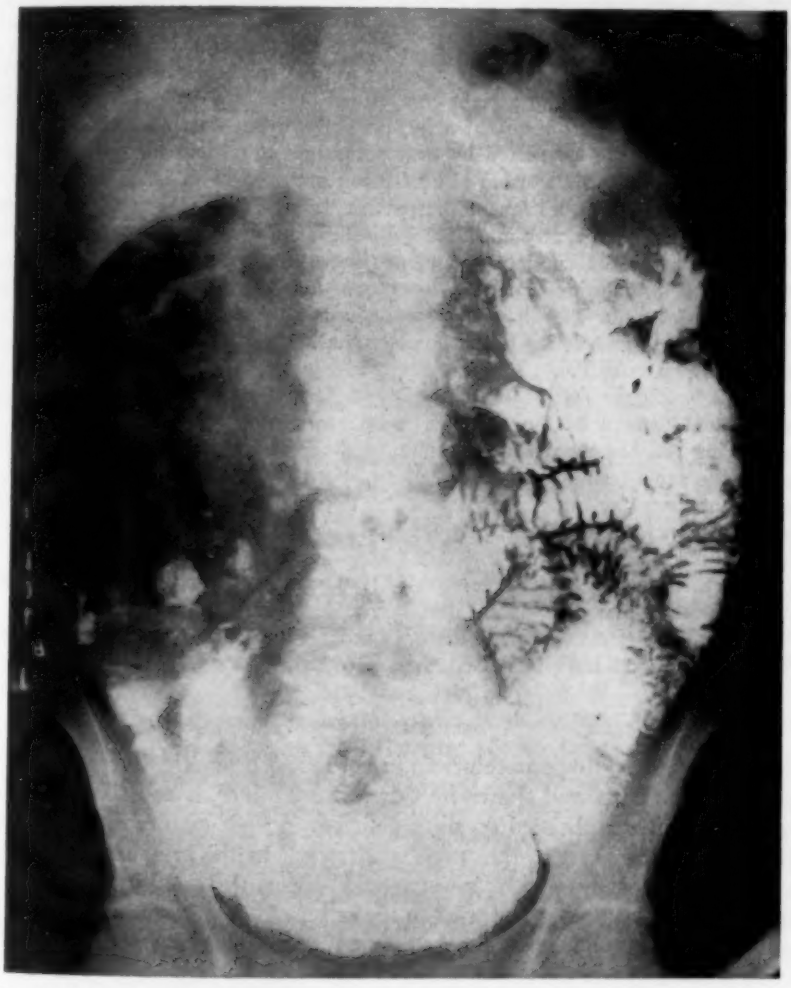

FIG. 4. July 27, 1950. Comparable film at height of ACTH effect, showing more rapid passage and more delicate mucosal pattern in jejunum (7/27/50). Both studies made by "rapid method" of small bowel study (Weintraub).

saline every six hours were begun, and on June 14 these were replaced, without her knowledge, by adrenocorticotropic hormone (ACTH, Armour), 25 mg. every six hours (figure 2). Twenty-four hours later, on June 15, she announced that she felt stronger and had a better appetite. Within a week her appetite became ravenous and her caloric intake was nearly doubled as compared with the control period. Though she had been passing six watery stools per day before ACTH, by the seventeenth day of treatment she was having but one or two small formed stools daily. At this time she had gained 10 kg. and was up and about the ward. With continued freedom from diarrhea and distention, and with good appetite and food intake, her weight rose to a maximum of 45.2 kg. on the forty-fourth day of treatment. Expressed in terms of standard height-weight tables, her weight increased under treatment from 50 to 75 per cent of the average normal.

On June 9, through error, the patient's usual dosage of calcium and vitamin D was discontinued, and on June 20 her serum calcium was 5.4, and Chvostek and Trousseau signs were strongly positive. With added calcium and vitamin D in her usual dosage the serum calcium level reached normal in three weeks. Also on June 20 (sixth day of ACTH), the patient complained of rapidly developing severe weakness, and blood chemistries revealed a hypokalemic, hypochloremic alkalosis of moderate degree. This was corrected by oral potassium salts, and her strength rapidly returned. There was no abnormal rise of blood pressure or of blood sugar.

Due to the critical condition of the patient before therapy, our efforts to obtain baseline data had to be greatly curtailed. The level of circulating eosinophils, which on admission was 3 per cu. mm., could not be used as an index of the additional adrenal cortical stimulation produced by exogenous ACTH. Neither the oral glucose tolerance tests nor the vitamin A absorption tests, performed before treatment, yielded satisfactory data which might be compared with the results of these tests after the treatment with ACTH. The barium study of the small bowel, however, performed on July 27, the forty-third day of treatment, showed a marked improvement in the mucosal pattern of the intestine, with more orderly and rapid passage, the barium having reached the ascending colon in three hours. In contrast, a study performed by the same technic two years before, when the weight and nutritional status of the patient were the same, had shown the flocculation of barium and the delayed propulsion characteristic of sprue, eight hours being required to reach the cecum (figures 3 and 4).

On the fortieth day of treatment, ACTH dosage was cut to 6.25 mg. every six hours. Beginning five days later, diarrhea and anorexia gradually returned. On the forty-ninth day treatment was discontinued. In the six weeks since that time, diarrhea and anorexia have increased, and there has been a weight loss of 6 kg.

Comment

The occurrence of hypoproteinemia in sprue has been widely recognized, and its frequency has been well shown by Garcia Lopez and his associates.[1] His patients, however, had subsisted on diets deficient in high quality protein for long periods prior to the onset of the sprue syndrome. In the present case, however, as in many other patients with "non-tropical" sprue, the quantity and quality of ingested protein had been good prior to the onset of the illness, and the hypoproteinemia is chiefly explained by general anorexia, profound diarrhea, and probable defective hepatic synthesis.

The restoration of normal levels of serum albumin in this patient by infusion of salt-poor human albumin was regularly associated with a brief but striking re-

mission of the sprue syndrome. This change was always delayed until the serum albumin level had risen well over 3.0 gm., and we believe it to be independent of therapeutic suggestion. In every instance, symptoms returned before the level of serum albumin began to fall again. When equally intensive administration of salt-poor albumin was begun in the face of a clinical relapse, but when the serum total protein and albumin values were normal, no therapeutic effect was obtained. From these facts it is inferred that the remission of symptoms was achieved by a sudden establishment of normal serum osmotic pressure, a condition noted by Verzár [2] as essential for normal intestinal absorption. It is conceived that once this shift in equilibrium had been accomplished, other factors governing rates of absorption soon changed for the worse, and the efficiency of the entire absorptive process was again compromised.

The use of ACTH in treatment of this patient was predicated upon two experimental observations. Verzár and McDougall [2] reported that the rate of absorption of glucose and of fatty acid from the small intestine of the rat was greatly diminished after adrenalectomy, and again increased upon the subsequent injection of adrenal cortex extract. This has been both confirmed [3, 4] and denied [5, 6] by others. Flat oral glucose tolerance curves are common to both Addison's disease and sprue, and Thorn and his associates [7] have commented on the diminished fat absorption in patients with Addison's disease. One may properly speculate whether the diarrhea and great loss of weight so commonly seen in Addison's disease may not be due to defective absorption. Paniagua,[8] however, did not find deficient adrenal cortical reserve in cases of tropical sprue. We have consistently found eosinopenia in the patient here reported during phases of severe illness, but observed a normal eosinophil count four days after ACTH therapy was ended. Accordingly, we believe that the patient's own adrenals respond well to the stress of her illness.

The basis for her clinical improvement during ACTH therapy is not certain. Although the patient knew she was to receive this hormone, she did not know when it was begun in the place of saline injections; yet she consistently dated her improvement from the first day of ACTH therapy. The rise in energy and spirits which usually follows the inception of ACTH treatment occurred here, and with it a striking increase in appetite. This led to rapidly improved nutrition, and it is possible that this alone was responsible for the remission of symptoms. On the other hand, she did not reach a higher level of nutrition, as judged by weight and energy, than had prevailed two years before, when her small intestinal roentgenograms had revealed a grossly abnormal pattern of motor function. The great improvement in this pattern during ACTH therapy is the only evidence that intestinal function was significantly and fundamentally altered.

No direct evidence has been adduced to show any actual improvement in intestinal absorption, and the rapid fall in serum calcium during ACTH therapy suggests that despite her general improvement she was still unable to absorb a large proportion of the calcium and vitamin D available in her intestine. It is possible, despite the long duration of the patient's illness, that her sprue syndrome is symptomatic of a lymphosarcoma of the intestine, and that the clinical results here described are due to the destructive effect of adrenal steroids upon that neoplasm. Further studies on the mechanism of this therapeutic effect, and on its application to other cases of nontropical sprue, are in progress.

SUMMARY

A case of severe idiopathic steatorrhea, resistant to conventional therapy, is reported. On three occasions, sudden elevation of the serum albumin from the subnormal to the normal range, by the use of plasma or concentrated salt-poor human albumin, effected a transitory remission of symptoms. Administration of ACTH for seven weeks produced striking increase of weight, disappearance of diarrhea, anorexia and distention, and marked improvement in the motor function of the small intestine. The possible mechanisms of these effects are discussed.

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VENTRICULAR ANEURYSM A CAUSE OF PERSISTENT RS-T SEGMENT DISPLACEMENT *

By ELWYN EVANS, M.D., F.A.C.P., *Orlando, Florida*

WILSON et al.[1] in their important paper, "The Precordial Electrocardiogram," described a case with persistent RS–T segment displacement and mentioned that in three cases of this sort, one seen by Langendorf, a ventricular aneurysm was present. On the basis of these observations, a tentative diagnosis of an aneurysm of the ventricle was made in a patient showing striking persistent RS–T segment displacement following typical acute posterior myocardial infarction. This diagnosis was later substantiated at autopsy.

CASE REPORT

A 50 year old white male was first seen in consultation on May 26, 1947, at which time he gave a history of having had substernal pain on exertion for five years. At 2 a.m. on May 16 he awoke with severe crushing substernal pain which radiated

* Received for publication April 23, 1949.

to both arms. The family physician made a diagnosis of and treated him for coronary occlusion. An electrocardiogram taken two days later showed no definite evidence of myocardial infarction. After several severe bouts of pain, the patient consented to enter the hospital on May 23. An electrocardiogram taken the day before (figure 1) showed no significant change from the one taken on May 18, but the tracing taken on May 25 revealed diagnostic evidence of a fresh posterior myocardial infarction. Q waves measured 2 mm. in Lead II and 9 mm. in Lead III. RS–T segments were elevated 1.5 mm. in Leads II and III and depressed 3 mm. in CF_2 and 2 mm. in $CF_{4 \text{ and } 5}$. T waves were inverted in Lead III. The sedimentation rate was 24 mm. and the white blood count 21,900, with 76 segmented cells, 13 stabs and 1 juvenile cell.

A portable chest roentgen-ray film showed moderate cardiac enlargement and pulmonary congestion.

When the patient was examined on May 26 he appeared quite comfortable. The blood pressure was 120 mm. Hg systolic and 72 mm. diastolic; the pulse was regular

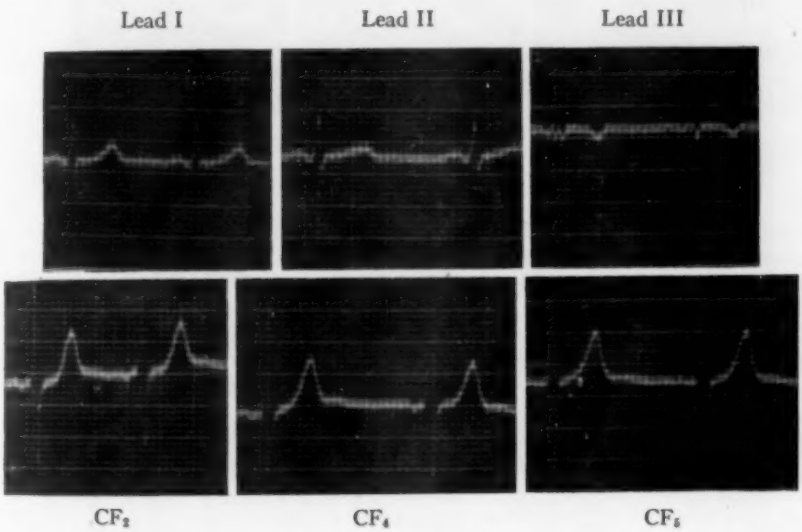

FIG. 1. May 22, 1947.

at 120. The temperature was 101.2° F. The neck vessels were normal. The apex impulse could not be seen or felt, and percussion was inaccurate because of abdominal distention. There was a grade I apical systolic murmur. The second pulmonic sound was greater than the second aortic sound. There were few basal râles. The liver was not enlarged and there was no edema of the legs. The remainder of the physical examination was not contributory.

Chest pain recurred on several occasions. Marked dyspnea appeared on June 5, when his white blood count was 17,200 although his temperature was normal. He was digitalized at this time. Other treatment included papaverine, vitamins, low salt diet, oxygen, Dicumarol, atropine, mercuhydrin and analgesics. An electrocardiogram (figure 2) showed large Q waves in Leads II and III and marked persistent RS–T segment displacement. The patient was allowed to go home on July 17 and was not seen again until September 12, when he complained of persistent pain in the left shoulder. Dupuytren's contracture was noted for the first time; it apparently appeared shortly after the patient left the hospital. A tentative diagnosis of a posterior

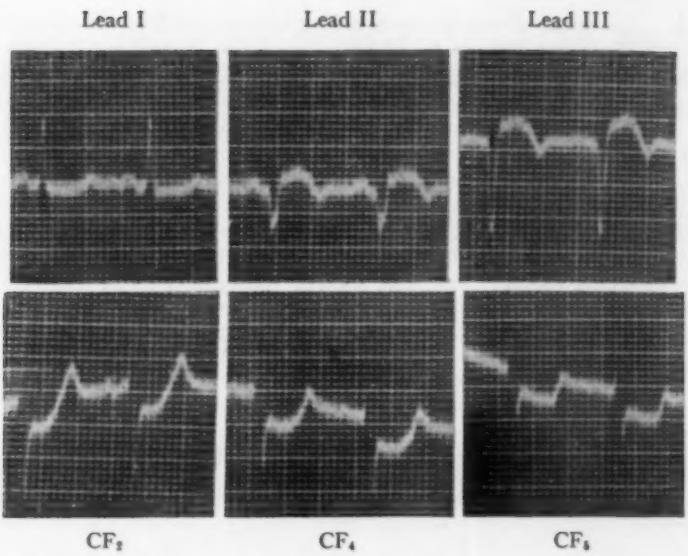

FIG. 2. June 5, 1947.

myocardial aneurysm was made because of persistently marked RS–T segment displacement in the electrocardiogram.

On October 10 he gave a history of having a little more tightness in his chest than usual. There was now a grade III apical systolic murmur and a gallop rhythm. The left border of cardiac dullness was just inside the anterior axillary line. The apical impulse was diffuse. There were râles throughout both lungs. The white blood count was 11,600, with 80 per cent polymorphonuclear and 6 per cent stab cells. Fluoroscopy revealed slight paradoxical pulsation of the left cardiac border in the supra-apical region. As the apex retracted, there was a slight outward thrust of the left heart border synchronous with aortic pulsation. An electrocardiogram (figure 3)

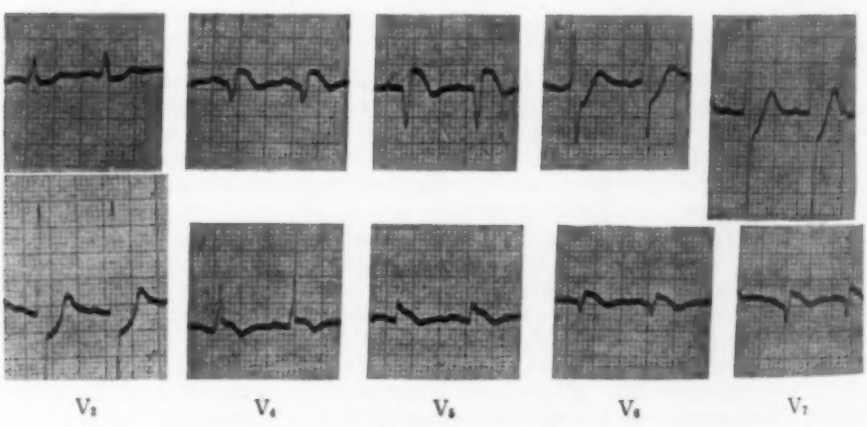

FIG. 3. October 10, 1947.

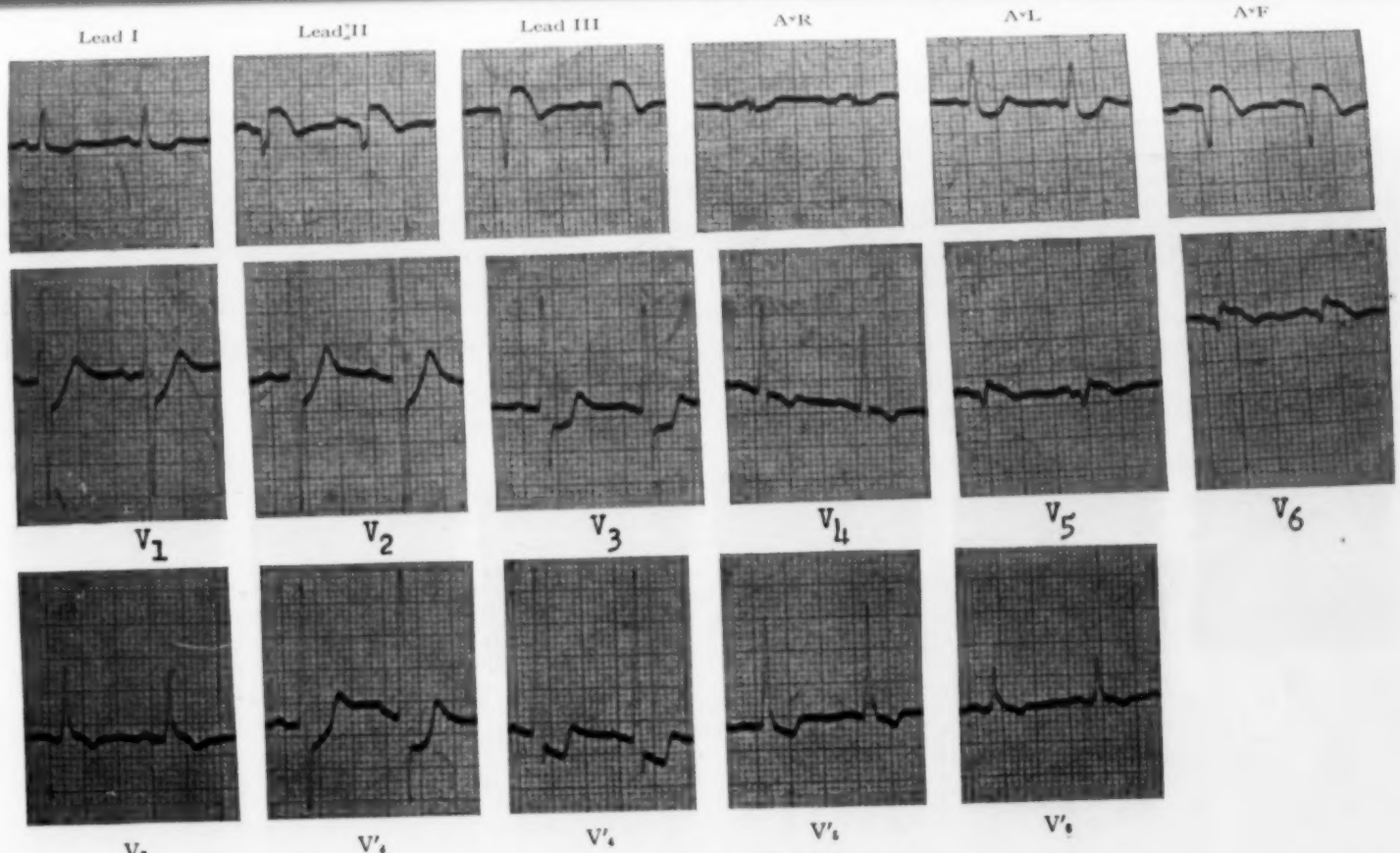

FIG. 4. October 18, 1947.

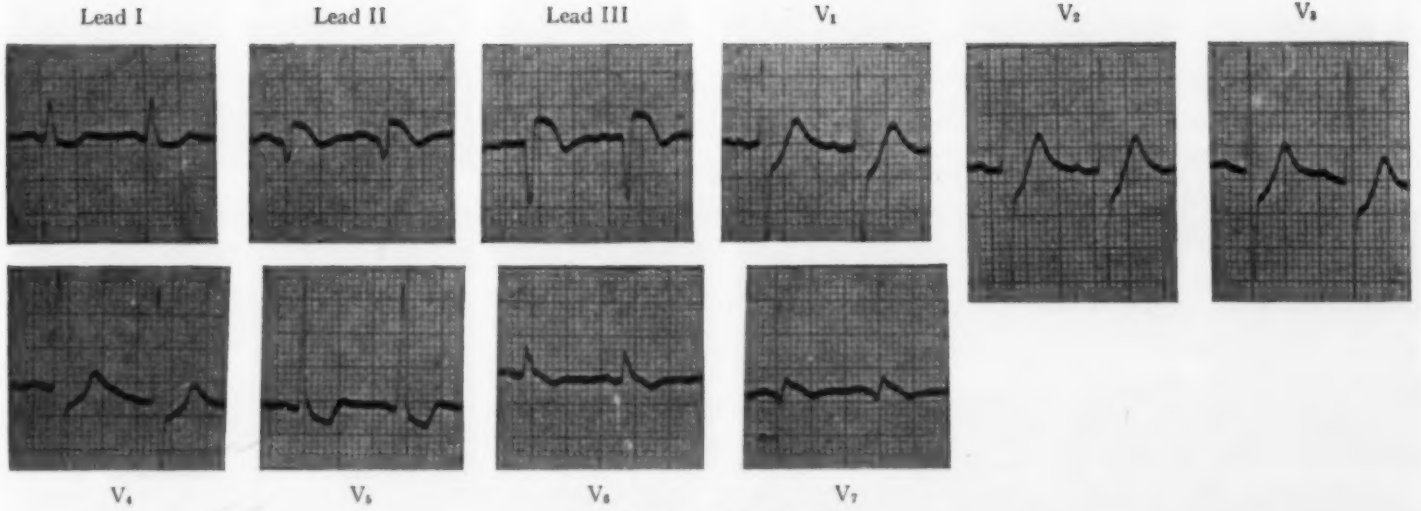

FIG. 5. November 28, 1947.

still showed large Q waves in Leads II and III, persistent marked RS–T segment displacement and evidence of fresh low lateral myocardial infarction. A tracing on October 18 (figure 4) showed little change from that taken on October 10, but the one taken on November 28 (figure 5) showed a return of the RS–T segments in the lateral positions, towards the isoelectric line. V′ chest positions in the tracing of October 18 were taken one level above the V leads, according to the terminology of Evans and Black.[2] $V'_{1 \text{ and } 2}$ were in the third interspace at the right and left sternal borders, respectively. $V'_{3 \text{ to } 7}$ were at their respective points one level above $V_{3 \text{ to } 7}$.

Unfortunately the patient died in my absence on December 5, and autopsy permission was not obtained until the patient was ready for burial. A partial postmortem examination by myself revealed a large ventricular aneurysm involving most of the posterior wall of the left ventricle. The ventricular wall was thin in this region and grossly appeared to be made up of scar tissue which was adherent to the pericardium. There was a large intramural thrombus. The heart was generally enlarged and weighed 810 gm. The left ventricular wall measured 25 mm. in thickness, the right, 8 mm. The right coronary artery, which supplied the posterior wall of the left ventricle, was completely occluded 6 cm. from the coronary ostium. Arterial supply of the lateral wall could be identified with difficulty, but occlusion of a small branch of the left circumflex artery apparently caused the low lateral infarction. Microscopic study of the midportion of the posterior wall of the left ventricle substantiated the gross impression. The thin ventricular wall was predominantly made up of collagenous scar tissue. A second section was taken from the lower anterolateral border of the aneurysm where it joined the region of the suspected low lateral infarction. Here the scar tissue appeared to be replacing myofibers. Interstitial hemorrhage of moderate degree without significant inflammatory reaction between muscle and scar tissue suggested a recent myocardial infarct.

Discussion

As mentioned in the introductory remarks, Wilson et al.[1] in their paper, "The Precordial Electrocardiogram," described a case with persistent RS–T segment displacement and stated that in three cases of this sort, one observed by Langendorf, a ventricular aneurysm was present. They also stated that this association was possibly due to chance and they knew of no reason why a ventricular aneurysm should displace the RS–T junction or deform the RS–T segment. Because of these observations and the presence of persistent, striking RS–T segment displacement in our case following an obvious posterior myocardial infarction, a tentative diagnosis of a posterior ventricular aneurysm was made.

Since Wilson's report, Langendorf has again observed RS–T displacement associated with ventricular aneurysm.[3] He stated that L. N. Katz thought such findings were caused by a current of injury in the myocardium surrounding the aneurysm. White [4] stated that there was no reason why an aneurysm should produce persistent RS–T segment displacement and that continued infarction or near-infarction was a possible cause. No RS–T displacement persisted in the electrocardiograms of his patient with the largest ventricular aneurysm. Nordenfelt [5] described large aneurysms of the anterior wall of the left ventricle which were characterized by relatively low R_1, deep $S_{2 \text{ and } 3}$, elevated RS–T segments in all leads and negative T_1, but stated that these findings were not sufficiently typical to make a definite diagnosis. Goldberger and Schwartz,[6] in their paper, "Electrocardiographic Patterns of Ventricular Aneurysm," do not mention RS–T segment displacement, although several of their illustrated cases showed elevation of

RS–T segments in precordial leads. They described the pattern with a small R_1, associated with deep $S_{2 \text{ and } 3}$, and the pattern in which main deflection was downward in the three standard leads, but stated that these patterns were not diagnostic because they sometimes occurred in myocardial infarction without aneurysm. Other authors,[7, 8] describing the electrocardiogram in ventricular aneurysm, also failed to mention RS–T segment displacement. Scherf and Boyd[9] stated that there was no typical electrocardiogram in ventricular aneurysm, but that it was remarkable how often a deep Q wave appeared in Lead I with a slightly elevated RS–T segment suggestive of a recent infarction, except that the pattern persisted for years. Rosenberg and Messinger[10] described electrocardiograms of eight patients with proved myocardial aneurysms, all of which showed Q waves and persistently elevated RS–T segments over the septal area and left side of the heart. The T waves were inverted or diphasic. It is of interest that these authors described evidence of anterior myocardial infarctions, Q waves in Lead I associated with persistent elevation of RS–T segments in this lead, or Q waves in the left precordium associated with persistently elevated RS–T segments in these leads, and that our case had a posterior myocardial infarction associated with persistent marked depression of RS–T segments in Lead I and precordial leads and elevation in Lead III.

Other causes of RS–T segment displacement did not appear to be primary in this case, although digitalis and pericarditis were probable contributory factors. The associated posterior pericarditis was thought to be secondary to the extensive infarction. Widening of the QRS complex or carcinoma of the heart[11] obviously were not factors in the production of the RS–T changes.

Paradoxical pulsation of the left cardiac border was at first thought to confirm the diagnosis of ventricular aneurysm, but this is not an infallible sign. Master[12] found that an outward thrust of the left cardiac border synchronous with retraction of the apex and pulsation of the aorta occurred in 50 per cent of 164 cases of coronary occlusion. The abnormal pulsations were apical or supra-apical in 85 per cent, and the location did not depend upon the location of the infarct as determined by the electrocardiogram. Paradoxical pulsations, however, have been found when specifically looked for in patients who have been proved to have aneurysmal dilation of the left ventricle.

Summary and Conclusions

1. Ventricular aneurysm is a possible cause of persistent RS–T segment deviation in the electrocardiogram and should be suspected if significant deviation persists.

2. In this case the posterior ventricular aneurysm, tentatively diagnosed on the basis of marked persistent RS–T segment displacement, was confirmed at autopsy.

The author wishes to express appreciation to Dr. Franklin D. Johnston, University of Michigan, for suggestions and criticism.

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PELVIC TUMORS WITH ASCITES, HYDROTHORAX, OR BOTH (MEIGS'S SYNDROME) *

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CONFRONTED with a female patient with a pelvic tumor and with ascites or hydrothorax, or both, one is prone to make a diagnosis of malignant tumor with metastasis. It does not appear to be generally known that benign pelvic growths may be associated with such accumulations of fluid, and that even when the tumor is malignant the fluid may not represent peritoneal or pleural involvement. It is the purpose of this report to call attention to such occurrences.

The point of greatest significance is the remarkable recovery of such patients following removal of the tumor when it is benign, and the failure of the fluid to return for months or years, at least in some cases, even though the tumor is malignant.

I. UTERINE TUMORS WITH ASCITES

In 1909 Kelly and Cullen [1] described cases of myoma uteri in whom there were large amounts of free ascitic fluid for no discernible reason. In 1915 Cabot [2] recorded such cases, and Salmon [3] added others in 1934. In these patients there was no recurrence of the fluid following removal of the tumors. Such cases must be extremely rare, as scarcely a day passes at the Medical College of Virginia hospitals without the removal of one or more fibromas of the uterus, and yet Hoge [4] can recall no such case.

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From the Medical Department of the Medical College of Virginia, Richmond, Virginia.

II. Ovarian Tumors With Ascites

Many writers [2, 5, 6, 7, 8] have noted the presence of inexplicable ascites with fibromas of the ovary. Similar fluid has been reported in other benign ovarian tumors, and in malignant ovarian disease without peritoneal metastasis, as cystoma,[2] multilocular pseudomucinous cyst,[9] theca and granulosa cell tumors,[10, 11, 12] fibroadenomas,[11] teratomas [13, 14] and fibrosarcomas.[9] In these cases the fluid failed to recur following removal of the tumor.

Our own material, though small, indicates that such findings are infrequent. Thus, of 12 cases of dermoid, five of teratoma, eight of cystadenoma, three of fibroma, two of endometrioma, four of cystoma and one of Brenner's tumor—35 cases—there were two cystic tumors with twisted pedicles and small amounts of ascitic fluid, and one teratoma with massive ascites.

This last case is detailed below, with the hope that such a possible diagnosis will be called to the attention of others, thus avoiding the delay and discomfort suffered by our patient.

Case Reports

Case 1. A 55 year old colored female entered St. Philip Hospital, Richmond, Virginia, on September 21, 1945, complaining of swelling of the abdomen and shortness of breath. About four months before admission she had noted painless swelling of the abdomen which gradually increased. Later she began to be short of breath and was particularly uncomfortable lying down. Several weeks before admission she noted slight swelling of the feet and ankles. As her abdomen enlarged she seemed to be losing flesh elsewhere.

In the past her health had always been good. She had had two normal pregnancies. Her menses had stopped in 1935. There was no history of alcoholism.

Physical examination showed a small, thin, weak-looking female sitting on the side of the bed in mild respiratory distress. She weighed 113 pounds and her temperature was 100° F., pulse 94, respirations 26 and blood pressure 110 mm. Hg systolic and 65 mm. diastolic. The heart and lungs were normal. The abdomen was tremendously distended with fluid. No masses or organs could be felt. There was slight pitting edema over the shins.

In the laboratory the hemoglobin was 78 per cent, red blood cells 5,040,000, and white blood cells 13,900, with 82 per cent polymorphonuclears. The urine showed a specific gravity of 1.026 and a trace of albumin, being otherwise normal. The blood sugar was 121 and the non-protein-nitrogen 28 mg. per cent. The icteric index was 9 units. The blood proteins were 5.5 gm. per 100 c.c., with albumin 2.7 and globulin 2.8. Both flocculation and complement fixation tests for syphilis were repeatedly positive. Roentgenogram of the chest showed a linear transverse shadow at the right base compatible with lung infiltration or collapse. The right costophrenic angle was obliterated.

Subsequent Course: On the afternoon of admission, abdominal paracentesis yielded 15,000 c.c. of clear yellow fluid, having a specific gravity of 1.026 and 200 cells per cu. mm. (type of cells not determined). This fluid contained "4 plus albumin." No organisms were demonstrated on smear or culture. Paraffin block sections of the centrifuged fluid showed no tumor cells.

Following aspiration, a hard, irregular, movable, slightly tender mass about the size of a baby's head was felt in the lower midabdomen. This mass was made up of five distinct "lobes" and seemed to be attached in the pelvis. On pelvic examination, a large, hard, irregular mass was felt posterior to the cervix.

The fluid rapidly re-accumulated and, during the ensuing week, three further tappings yielded abundant similar fluid, with a specific gravity on one occasion of 1.017.

The patient was discharged on the eighth hospital day to receive symptomatic aspiration in the Out-Patient Department. The diagnosis on discharge was malignant tumor of the ovary with abdominal and possibly pulmonary metastases. A member of the house staff suggested Meigs's syndrome.

During the next 18 months, from October, 1945, to March, 1947, her abdomen was aspirated approximately every 30 days, 11,000 to 15,000 c.c. of clear yellow fluid being obtained each time. Its specific gravity varied from 1.014 to 1.020. A second study was negative for tumor cells. The lower abdominal mass did not change perceptibly. After aspiration the liver edge could be felt three to four fingerbreadths below the costal margin in the right midclavicular line. It was smooth and nontender. On one occasion fluoroscopy of the chest showed a semilunar density obscuring the right diaphragm.

By March, 1947, the patient's condition had become pitiful in the extreme. She had lost an additional 30 pounds since leaving the hospital in October, 1945, and resembled a skeleton with a large abdomen. At home she was miserable save for short periods immediately following aspiration. Getting to the Out-Patient Department was an almost overwhelming effort.

On March 14, 1947, she was readmitted for the insertion of a Crosby [15] button with the hope that she might be symptomatically relieved. At this time her hemoglobin was 72 per cent, red blood cells 3,090,000, and white blood cells 8,900, with 80 per cent polys. The urine was normal. The non-protein-nitrogen was 29 and the blood protein 4.7, with 2.1 albumin and 2.5 globulin. The serologic test for syphilis was again positive. Roentgenogram of the chest was normal, the right lower lung field density having cleared.

On the surgical service, Dr. H. C. Lee felt that no definite diagnosis had been made, that Meigs's syndrome was certainly a possibility, and that the patient should be explored. After a transfusion of 500 c.c. of whole blood, this was carried out on April 8, 1947. At operation, after aspiration of 3,000 c.c. of thin brownish fluid, a large nodular, cystic and semi-solid mass was found arising from the left ovary. The uterus contained numerous fibroids varying up to 4 cm. in diameter. The peritoneum was free of nodules, as was the liver, which was smooth, soft and granular. Appendectomy, supravaginal hysterectomy, and bilateral salpingo-oöphorectomy with removal of the tumor were done.

The pathologic report of these tissues showed a normal appendix and right ovary. The uterus contained numerous fibroids. The tumor and left ovary weighed 500 gm. The cut surface showed different areas appearing as ovary, thyroid, cartilage and bone. Microscopically, some sections showed ovarian stroma containing large and small glandular or cystic structures lined with columnar cells, some revealing endometrium and others having a mucoid secretion; in other areas, there was dense hyaline fibrinous tissue with calcification and deposits of cholesterol. There was an abundance of adenomatous thyroid tissue. A diagnosis of teratoma of the ovary was made.

It is difficult to describe the remarkable postoperative improvement. Almost immediately she began to feel better and developed a ravenous appetite. The ascites did not recur. Three months later she seemed entirely well and had gained 25 pounds. The liver edge was still palpable.

Since that time, a period of two years, she has continued in apparently perfect health, has worked regularly, and has gained 78 pounds.

III. Uterine and Pelvic Tumors With Ascites and Hydrothorax, or Hydrothorax Chiefly, Meigs's Syndrome

The greatest credit is due to Meigs who, in 1937 [16] and thereafter,[17, 18] called attention to cases of ascites and hydrothorax associated with fibromas of the ovary in whom these fluid accumulations disappeared and did not recur after removal of the tumor. Although similar isolated cases [2, 7, 19, 20, 21, 22, 23] had been previously recorded, the report of Meigs and Cass served to focus attention on the syndrome which now bears the former's name. In some of these patients the presenting findings suggested primary pulmonary or pleural disease, the ascites being of very small degree or absent.

Despite Meigs's statement [25] that this syndrome applies only to solid tumors of the ovary, the tendency now is to classify under this heading any pelvic tumor, benign or malignant, associated with hydrothorax, ascites, or both, where no ostensible explanation, such as metastasis, can be found for these accumulations of fluid. Fibromas (solid, cystic or hemorrhagic), papillary cystadenocarcinoma, granulosa cell tumors, theca cell tumors, multilocular cystadenomas, adenocarcinoma, dermoids (fibromas also present), Brenner's tumor, multilocular pseudomucinous cystadenoma, teratomas, and uterine fibroids have been so classified. Under such a broad heading some 70 cases [3, 7, 8, 10, 11, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56] can be found in the literature. We are adding the following case.

Case 2. A 56 year old white female entered the Medical College of Virginia Hospital, Richmond, Virginia, on December 8, 1944, complaining of swelling of the abdomen and ankles for several weeks. About four weeks before admission she began to have dull aching pain through the small of her back. This pain was worse at night. Two weeks later she noticed swelling of her abdomen, which gradually increased and was followed by swelling of both feet and ankles. She felt that she had lost weight, but had not been weighed.

The history was otherwise insignificant except for "fainting spells" occurring once or twice a year for many years. Her periods had stopped in 1935, but six months and again four months before admission there had been a small amount of bloody vaginal drainage which lasted several days.

Physical examination showed a thin, middle-aged woman in no acute distress. Her temperature was 98.6° F., pulse 75, respiration 22, and blood pressure 110 mm. Hg systolic and 80 mm. diastolic. There was dullness over the right lower chest, where the breath sounds were absent. The heart and lungs were otherwise normal. The abdomen was greatly distended with fluid. There was moderate pitting edema of both lower extremities.

In the laboratory the hemoglobin was 76, red blood cells 3,600,000, and white blood cells 10,350, with 81 per cent polymorphonuclears. The urine showed a specific gravity of 1.030, and a trace of acetone, being otherwise normal. The blood sugar was 85 and non-protein-nitrogen 46 mg. per cent. The total proteins were 5.5 gm. per cent with 3.1 albumin and 2.4 globulin. The serologic test for syphilis was negative.

Course in Hospital: On the day after admission, abdominal paracentesis yielded 6,000 c.c. of brownish fluid, having a specific gravity of 1.015, sugar of 95, chlorides of 640, protein of 4 gm. per cent, and 53 white blood cells not otherwise identified. No organisms were seen on smear and the culture was negative. Pelvic examination showed an orange-sized, rather fixed nontender mass in the right pelvis. It was thought that a small uterus could be felt separate from this mass.

On December 12, 500 c.c. of straw-colored fluid were removed from the right chest. This had a specific gravity of 1.015, chlorides 644, sugar 101, protein 1.4 mg. per cent, and 310 cells, polymorphonuclears 2 per cent, lymphocytes 32 per cent, endothelial 66 per cent. Paraffin block sections of the centrifuged fluid showed no malignant cells. No organisms were seen on smear and the culture was negative. Roentgenogram of the chest the following day was normal except for slight blunting of the right costophrenic angle.

By December 16, 1944, the ascites had re-accumulated; on December 20 she was surgically explored and 4,500 c.c of thin, blood-tinged fluid were removed. Both ovaries contained large, hard tumor masses, the right being 12 by 10 by 6 cm. and the left, 8 by 4 by 3 cm. There were adhesions to the surrounding peritoneal surfaces, but the peritoneum in general and the liver appeared normal. There was a large, smooth, retroperitoneal mass in the upper midabdomen.

Both ovaries and tubes were removed. The upper abdominal mass was explored and a piece of tissue taken. This mass was quite friable and bleeding was difficult to control. The pathologic report was papillary adenocarcinoma of both ovaries with metastases to the retroperitoneal lymph nodes.

During the following seven months, until August, 1945, she was periodically examined, including pelvic examination, without abnormal findings. At that time a mass was felt in the upper middle right abdomen, which appeared to arise approximately in the location of the retroperitoneal mass found at operation. At no time was there any suggestion of reaccumulation of the fluid.

During the following year, until August, 1946, she remained well. The abdominal mass was always palpable but did not appear to change. At this time a hard, nontender, fixed, egg-sized mass was noted behind the left sternomastoid muscle. There was no suggestion of ascites, pelvic examination was negative, and she felt quite well. This mass in the neck regressed slightly following roentgen-ray treatment.

In May, 1947, over two years after operation, the mass in the abdomen had enlarged considerably and there was generalized abdominal swelling, apparently due to ascites. The mass in the neck was little changed. A new mass was felt in the left axilla and there were several small hard nodes above the left clavicle. She suffered considerably with pains in her legs and there was slight edema of the ankles.

Thereafter her course was gradually downward, with increasing ascites, edema and weakness. Aspiration was never again necessary. Her appetite and spirits remained good. Death occurred peacefully in February, 1948, 38 months after operation.

Summary and Discussion

We have reported: (1) A patient with an ovarian teratoma, largely composed of thyroid tissue, associated with massive recurrent ascites, in whom the fluid did not re-accumulate and whose health was restored after removal of the tumor. On several occasions small amounts of fluid were suspected in the right pleural cavity, but hydrothorax was not a particular feature of the case. (2) A patient with papillary adenocarcinoma of the ovaries and retroperitoneal lymph nodes, with ascites and hydrothorax, but with normal peritoneum at operation and without roentgen-ray evidence of pleural or pulmonary metastases, in whom the fluid did not re-accumulate for 29 months after removal of the tumors, despite transperitoneal biopsy of the retroperitoneal mass.

From a review of the literature and our own material, it appears that fibroids of the uterus and ovarian tumors of many types, both benign and malignant, may develop inexplicable ascites, hydrothorax, or both. In some cases this fluid has been bloody.[3, 8, 10, 29, 30] The basis for its formation remains obscure. In two

cases Meigs [18] demonstrated that the fluid passed from the abdominal to the pleural cavity. Not only is the cause of its occurrence unknown, but why some cases show little or no ascites but massive hydrothorax [10, 16, 26, 29, 34, 38, 41, 43] is even more difficult to understand.

Since the term "syndrome" indicates a group of clinical or other findings occurring together, and since all cases of the type described above have the fundamental likeness of pelvic tumor and body cavity fluid, it appears desirable to broaden the term "Meigs's syndrome" to include all cases of pelvic tumor, benign or malignant, solid or cystic, with ascites alone, hydrothorax chiefly, or both, in whom no ostensible explanation, such as metastasis, can be found for these accumulations of fluid. By definition, this fluid should be "cured" by removal of the tumor. In malignant tumors with later spread to the peritoneum the fluid may recur, as was probably the outcome in case 2.

From the standpoint of diagnosis, such a broad use of the term might put us on the alert whenever we encounter a woman whose difficulties center around ascites, pleural effusion, or both. As noted in the literature and illustrated by case 1, these patients have all too often been put aside as cases of hopeless malignant disease.

Exploratory laparotomy is recommended in all patients showing a pelvic mass and ascites, hydrothorax, or both. The finding of a primary tumor elsewhere, such as in the stomach, would, of course, alter this recommendation.

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CORTONE IN LYMPHOBLASTOMA: A CASE REPORT*

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THE following case of lymphoblastoma, in which Cortone was used only after all accepted methods of treatment had failed, is reported because the drug is new and because the literature contains few such accounts.

CASE REPORT

The 48 year old owner and manager of a paper box business was first seen by me in October, 1948. The family history was negative except for the fact that one sister was dying of cancer of the breast. The patient was married and had two children, both living and well. He had never been ill, and had been working very hard for the past 10 years, often as much as 15 hours or more a day. The patient had felt perfectly well and apparently had had a great deal of energy and stamina until two months previously, when he lost ambition and strength to the point of being barely able to do his work. His appetite became poor and there was a weight loss of 22 pounds. At times he would get very warm and feel that he had some fever; he also noticed that he had become rather pale. He stated that he often suffered with a mild generalized pruritus, although there had never been any skin rash. His sleep was fitful and he had nocturia three or four times a night. He often changed his pajamas two or three times because of profuse perspiration. Recently, he had become very irritable and nervous.

Physical examination revealed an apparently acutely ill adult male with a rather pale, extremely sallow skin. He was six feet tall and weighed 135 pounds (a loss

* Received for publication December 14, 1950.

of 22 pounds). His temperature was 99.2° F., pulse 100, and respirations 20. A thorough physical examination, including the nervous system, was completely negative. Special attention was given to the presence of any glandular enlargement but none was found. The spleen and liver were not palpable and seemed normal in size. Because of his symptoms careful examination was made of his chest but there were no signs of any pulmonary lesion. At that time, the blood culture, blood sugar, blood urea nitrogen, alkaline phosphatase and cephalin flocculation were all normal. The urine was chemically and microscopically negative. Urobilinogen was present in the urine only in normal dilutions. The icterus index was 4, and red cell fragility showed a normal curve. There was no cough, and stomach washings on three occasions were negative for acid-fast bacilli. Roentgenogram of the chest revealed no abnormality of the lungs, heart or mediastinum. Sedimentation index was increased to 5 (normal being 2). Complete blood count revealed a simple moderate hypochromic anemia; red blood cells, 3,900,000; hemoglobin, 11 gm.; mean corpuscular volume, 82 microns; hematocrit, 35; white blood cells, 6,800 with polymorphonuclears, 62 per cent; small lymphocytes, 32 per cent; large lymphocytes, 5 per cent; and eosinophils, 1 per cent.

The findings were insignificant compared with the severe symptoms which this man presented. He seemed to be suffering from a severe illness, probably some blood dyscrasia, but no diagnosis was made at this time either from the physical examination or from the laboratory reports. A hematemic was prescribed and the patient was told to report back in several weeks. When he reported at that time and said that he felt much worse, he was hospitalized. There were no important changes found at this time except that a solitary lymph gland was discovered in the left axilla. This gland was removed for biopsy, and the microscopic diagnosis was definitely Hodgkin's disease.

The patient received a course of deep roentgen-ray therapy over the left axilla and over the spleen, which had now become just barely palpable, but at the end of two months he had lost more weight. The anemia had progressed and he was rapidly losing ground. A few more glands were now palpable in the left axilla and in both anterior triangles of the neck. At that time, nitrogen mustard was taking the place of radioactive phosphorus in the treatment of lymphoblastoma, and the patient went to New York where he received a course of nitrogen mustard treatments and several blood transfusions. He returned much improved and able to go back to work. The glandular enlargement in the neck and left axilla had disappeared, and the spleen had returned to normal size, or at least was no longer palpable.

Over a period of about a year and a half the patient went regularly to New York for nitrogen mustard treatments and transfusions. However, although there were no further glandular enlargements, the spleen again became palpable, the periods of well being became shorter and he experienced less and less relief. His red count began to drop rapidly, so that he required several transfusions between the nitrogen mustard treatments, which he received about every eight weeks. He gradually lost weight, his appetite deteriorated and he began to run fever of the Pel-Ebstein type. There were still no enlarged external glands, but the spleen had gradually increased in size and was now about three fingerbreadths below the costal margin.

By June, 1950, his red count was down to 2,000,000, and he was hospitalized locally. He now weighed only 110 pounds and was practically bedridden. During this hospitalization he received a total of 20 micrograms of nitrogen mustard and transfusions of whole blood totaling 3,000 c.c. In about 10 days he felt much improved and, when discharged, had a red cell count of 4,500,000 and a white count of 5,200 with a normal differential. It is remarkable that, with all the nitrogen mustard he received during the one and a half years of treatment, there was never much difficulty encountered because of marked reduction of either white cells or platelets. A close watch had been kept on these blood factors. The lowest white

cell figure during this period was 2,800 and the lowest platelet count was 55,000. I might add that in April, 1950, the patient had suffered for several weeks with herpes zoster of the right side of the face, a not uncommon complication of lymphoblastoma. The condition was effectively controlled by injections of Protamide.

By August, 1950, he had lost all the effects of his hospitalization in June. His red count was down to 1,600,000, his weight to just under 100 pounds. The skin itch had returned without any skin manifestations, and pains in the bones of the legs, spine and thorax, of which he had complained only slightly during his illness, now became most severe and required a narcotic for relief. He was so weak he was unable to get out of bed.

The patient was not aware of the seriousness of his condition but his wife was. At that time, Cortone became available and its use was proposed on a trial basis. Treatment was started on September 6, 1950. Cortone was administered in 25 mg. doses by hypodermic every four hours day and night for five days, then every six hours for five days, followed by every eight hours for five days and, subsequently, every 12 hours, which dosage and frequency are still maintained. To prevent the pain and soreness produced by injections of which the patient complained bitterly, 1 c.c. of 2 per cent procaine was added to each dose of Cortone.

The improvement in the patient's general status, his feeling of well being and actual blood picture were amazing, particularly when we keep in mind that we were dealing with a late case of lymphoblastoma that had not responded to other treatment, and that the patient had been almost moribund.

He received only one pint of blood on the day of the first treatment, and from that date to the time of this report (see chart) his blood count has gradually returned to approximately normal levels. He received no other medication during the Cortone

CHART I

Date 1950	Blood Cl.	Blood K	Pl. Prot.	B.U.N.	C.B.C.	W.B.C.	Intake	Output	Wt. Lbs.	Blood Chlst.	Blood Sugar
Sept. 15	560	3.1	5.V%	13	1.6	2,300	800 c.c.	500 c.c.	91	90	78
Sept. 21	580	3.4	5.1V%	12	1 pt. bl. 2.4	2,500	1,875 c.c.	1,230 c.c.	94	93	110
Sept. 30	580	3.4	5.0V%	14	2.7	3,200	2,250 c.c.	2,140 c.c.	98	97	130
Oct. 8	600	3.2	6.V%	16	3.1	2,800	2,625 c.c.	2,070 c.c.	101	104	136
Oct. 16	550	3.6	6.V%	11	3.4	4,000	2,470 c.c.	2,000 c.c.	106	106	130
Oct. 24	560	3.6	6.8V%	12	3.4	4,200	2,820 c.c.	2,190 c.c.	110	122	124
Oct. 30	560	3.4	6.8V%	12	3.8	4,600	2,340 c.c.	1,980 c.c.	113	143	144
Nov. 10	550	3.6	7.V%	10	3.9	6.000	2,580 c.c.	2,370 c.c.	117	168	136
					Stopped Cortone						
Nov. 17	600	3.9	7.6V%	11	4.2	7,500	1,900 c.c.	1,730 c.c.	120	194	124
					Started Cortone						
Nov. 24	600	3.6	7.5V%	10	4.23	7,600	2,400 c.c.	1,960 c.c.	121	196	138
Nov. 30	580	3.8	7.6V%	10	4.2	7,400	2,230 c.c.	1,990 c.c.	123	192	132

treatment except sedation for the bone pains during the early part of the Cortone course.

Within a week all his pains disappeared. From a condition in which he was taking almost no food or liquids, his appetite improved to the point where he was being fed every two or three hours, and he stated, "I can't seem to get enough to eat." His pallor gradually changed to a warm, fairly good color. The pulse, which had been rapid and thready, became slower and of good volume, and his blood pressure rose from 90 mm. Hg systolic and 70 mm. diastolic to 130/90. The gain in weight was so rapid that, although there was no evidence of edema, it was feared that fluid was accumulating and on several occasions the Cortone therapy was interrupted, but no diuresis or weight loss occurred even after an intramuscular mercurial. The patient developed a mild euphoria.

From the chart it can be seen that his blood chemistry gave us very little trouble. On one occasion the blood sugar rose to 144 mg., but for the most part it ranged around 135 mg.

On November 30, 1950, his blood potassium was about 4 for the third consecutive week, and intake of potassium chloride was reduced from 15 gr. to 10 gr. daily. Although his blood cholesterol rose from 90 to 192 during the period of treatment, I cannot corroborate the findings of Adlersberg, Schaefer and Drachman [1] that Cortisone raises the blood cholesterol. The patient was so emaciated at the beginning of the treatment that his rise in blood cholesterol might have been a natural process produced by his excessive appetite.

At the time of this report there is no glandular enlargement, externally or mediastinally. The liver is not palpable and the spleen is just barely palpable. During the course of treatment the patient was kept on a low salt diet (about 1 gm. daily); potassium chloride was given in 15 gr. doses, which were then reduced to 10 gr. and have now been discontinued, because his food intake itself probably supplies sufficient potassium. There were no facilities for doing complicated nitrogen balances, but it is felt that the patient is in positive balance. The intake and output of fluids were measured at all times, although perhaps a little roughly, but the output was commensurate with the intake. The drenching perspirations which he suffered at night disappeared completely. The fever, which at times had been Pel-Ebstein's, became normal. The bone pains ceased after a week's treatment. He gradually became stronger, began to sleep well and, after a month's treatment, returned to part-time work. At the present time he is taking full care of his business and working 10 to 12 hours a day without undue fatigue.

This case seemed worth reporting because of the patient's dramatic return to health, but a relapse would not be unexpected.*

Conclusions

A case of proved lymphoblastoma is reported which had not responded to other therapeutic measures and was progressing to its terminal phase, but with the use of Cortone showed a dramatic improvement in physical status, blood picture and general well being of the patient. The response was almost immediate, and for the last six weeks the patient has been enjoying nearly normal health. The improvement has now lasted for over three months without signs of relapse.

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* On February 12, 1951, six months after the beginning of Cortone treatment, the patient is still in excellent health with no sign of relapse.

EDITORIAL

ION EXCHANGE RESINS

THE recent introduction into clinical medicine of a group of substances known as ion exchange resins has provided the physician with a new type of diagnostic and therapeutic tool. The principle of action of these substances differs in many respects from customary therapeutic agents. Moreover, the basic mechanism provides a versatility, the potentialities of which have only begun to be tapped. Although they can hardly be viewed, at this time, as having achieved an established place in the therapeutic armamentarium, a brief survey of recent studies with ion exchange resins will serve not only to elucidate their mode of action, but possibly also to indicate further fields of clinical usefulness.

The phenomenon of ion exchange has been employed empirically for many centuries, but recognition of its nature is generally attributed to Thompson and Way,[1] English agricultural chemists, who, in the middle of the nineteenth century, noted that treatment of a soil with either ammonium sulfate or ammonium carbonate resulted in the adsorption of ammonium ions and the release of calcium ions from the soil. Subsequently, it was discovered that the agents responsible for this reaction were naturally occurring sodium aluminum silicates. Silicates and other materials have been employed for a number of years in many phases of industrial chemistry. A familiar application of ion exchange is the process of "water softening" which involves the adsorption of calcium, magnesium, and other ions from "hard water" and their replacement by sodium ions contributed by the ion exchange material. In 1935, Adams and Holmes [2] observed that certain synthetic resins were capable of exchanging ions. The versatility of these resins was rapidly recognized with the result that a large number of new and unique uses were found for them in many fields of chemistry. Furthermore, the possibility of synthesizing new resins in the laboratory with certain "tailor-made" properties for specific purposes became theoretically attainable.

Among several theories of their mode of action is the crystal lattice theory.[3] The modern concept of ionic solids visualizes them as being completely dissociated. Thus, a crystal of sodium chloride contains no molecules of sodium chloride, but only sodium and chloride ions. Each ion of the crystal is surrounded by a fixed number of ions of the opposite charge. Each grouping is subject to certain attractive forces which are dependent upon the relative charges of the ions and the distance between them. It follows, therefore, that an ion at the surface of a crystal is subject to less attractive forces than a similar ion beneath the crystal surface. If placed in a medium such as water, the net attractive forces binding the ion to the

[1] Way, J. T.: On the power of soils to absorb manure, J. Roy. Agr. Soc. Eng. 11: 13, 1850.

crystal are diminished to such a degree that an exchange of this ion for another ion, or reaction with another ion in solution, is quite possible. Thus the reaction between sodium chloride in solution and added potassium nitrate may be looked upon as ion exchange. The ions of a solid can also be exchanged under two conditions: (*a*) if the material is so finely ground that an electrolyte solution can come in free contact with its ions, or (*b*) if the structure of the material is sufficiently porous so as to permit an exchanging ion to diffuse through it.

The various ion exchange resins, although not crystalline, permit diffusion of electrolyte solutions throughout their entire structure and thereby afford opportunity for ion exchange. They are, themselves, inert and highly insoluble in all ordinary solvents. Two general types have been synthesized: (1) cation (positive ion) exchange resins which have the property of exchanging one cation for another; (2) anion (negative ion) exchange resins which possess the property of adsorbing acid radicles.[4]

Cation exchange resins owe their reactivity to various functional groups, one of which is the carboxylic grouping (COOH). The mechanism of action of a carboxylic cation exchange resin may be schematically represented in the following manner:

R–COOH —in this form, or cycle, of the resin the cation, hydrogen (H^+), is capable of being exchanged for another cation.

R–COONa—the sodium form of a carboxylic cation exchange resin (R).

A typical reaction:

$$R\text{–}COONa + KCl \rightarrow R\text{–}COOK + NaCl.$$

As will be noted below, cation exchange resins have been employed clinically, in their ammonium, potassium, and hydrogen forms.

The action of an anion exchange resin may be schematically represented in the following way:

$$RX + HCl \rightarrow RX \cdot HCl$$

RX = resin with acid binding substituent. The reaction, as represented, cannot be viewed as ion exchange, but rather as acid adsorption. Newer evidence, however, indicates that true ion exchange does occur with anion exchange resins.

A discussion of the physico-chemical laws governing the behavior of ion exchange resins is beyond the scope of this brief presentation. Suffice it to say that the ion exchange capacity of a resin can be quantitated in vitro and is customarily expressed in milliequivalents per liter (mEq./L.) of ion exchanged or adsorbed per gram of resin.

[2] Adams, B. A., and Holmes, E. L.: Absorptive properties of synthetic resins, J. Soc. Chem. Ind. **54**: 1T, 1935.

[3] Bragg, W. L.: Atomic structure of minerals, 1937, Cornell University Press.

[4] Kunin, R., and Myers, R. J.: Ion exchange resins, 1950, John Wiley & Sons, N. Y.

In 1944, Steinberg,[5] reported on the use of a cation exchange resin in its sodium form or cycle for the prevention of coagulation of blood samples. The particular resin used had an ion exchange capacity of 2.2 mEq. of calcium per gram of resin. Blood allowed to flow through the resin was deprived of its calcium and thereby rendered incoagulable. Resin treated blood was found entirely satisfactory for hematological, serological and biochemical examinations. Furthermore, after use the resin could be regenerated—i.e. flushed with sodium chloride solution, and repeatedly used without exhausting its exchange properties. This particular medical application illustrates, in its simplicity, some of the basic principles of ion exchange resin behavior. The procedure has recently been employed in the collection of whole blood for transfusion purposes in conjunction with newly-designed plastic tubing and a plastic container. The possibility of increasing the stability of the formed elements of blood in vitro by this method is under study at present.

Beginning with the paper of Segal et al. in 1945 [6, 7, 8, 9, 10, 11] a series of reports has appeared regarding the use of various commercial anion exchange resins in the management of peptic ulcer. The substances used have exhibited no evidence of toxicity in rats, dogs and humans. Because their mode of action is different than other antacids—i.e. they adsorb rather than neutralize hydrochloric acid—they are said to prevent the acid rebound phenomenon common after the use of some alkalies. No disturbance of electrolyte balance in the blood was noted by any of the investigators nor was there said to be any evidence of undesirable adsorption of other essential elements from the lumen of the intestinal tract. Bargen [12] has recently commented upon the fact that ion exchange resins unlike other antacids have no constipating effect. He also noted their usefulness in combating the symptoms of ulcerative colitis and peptic ulcer when both occur in the same patient. Bargen has employed ion exchange resins in the control of skin irritation about the opening of entero-abdominal fistulas. Survey of the literature to date leaves the impression that although anion exchange resins can be usefully employed in the management of peptic ulcer symptomatology,

[5] Steinberg, A.: A new method of preventing blood coagulation, Proc. Soc. Exper. Biol. and Med. **56**: 124, 1944.

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[12] Bargen, J. A.: Anion exchange resins in the digestive system, Gastroenterology **16**: 507, 1950.

they possess no marked advantages over other modern forms of therapy. Additional experience will certainly be desirable to settle the matter definitively.

A new diagnostic use for ion exchange resin has recently been reported by Segal and his co-workers.[13] Using a carboxylic cation exchange resin, these workers substituted for the hydrogen a quinine radicle as an indicator compound. In the presence of hydrochloric acid this radicle will be liberated and promptly absorbed from the intestinal tract. It can be demonstrated in the urine within one to two hours after ingestion of the resin. Thus, without intubating the patient it is possible to determine the presence or absence of free hydrochloric acid in the stomach. The authors suggest the possibility of the use of this method in mass surveys to detect achlorhydric individuals.

The close interrelation of sodium metabolism with the movement of water in the fluid compartments of the body has been known for many years. Sodium retention is commonly associated with the abnormal retention of fluid in the body. In the management of such conditions as cardiac failure the achievement of a negative sodium balance is an important therapeutic aim. Two methods usually employed are rigid restriction of sodium chloride intake and the frequent use of mercurial diuretics which impair the tubular reabsorption of this cation. The difficulties associated with prolonged maintenance of a low sodium intake are well known to the clinician. In the effort to limit the salt intake to 0.3 to 0.5 gm. per day the diet which must be employed is usually unpalatable and monotonous. Failures are frequent. Moreover, the variability of the sodium content of many foods from time to time renders the problem difficult even under the best control conditions. The frequent use of mercurial diuretics is attended by some inconvenience, at best, and, occasionally, by toxic reactions. Hence the successful use of a cation exchange resin to achieve a negative sodium balance would represent a distinct therapeutic advance.

In 1946, Dock [14] reported the use of a cation exchange resin for this purpose. His initial studies in rats were sufficiently encouraging to suggest clinical investigation. Dock suggested that the use of two ounces per day of the resin he employed would permit a dietary intake of 3 gm. of sodium chloride per day and yet maintain a negative sodium balance. In 1949, Irwin et al.[15] presented a very complete study of electrolyte balance in a non-edematous individual as well as in several patients with congestive heart failure and a patient with advanced cirrhosis of the liver all of whom were treated with a cation exchange resin. The observations reported by these

[13] Segal, H. L., Miller, L. L., Marton, J. J., and Young, H. V.: The use of cation exchange indicator compounds to determine gastric acidity without intubation, Gastroenterology **16**: 380, 1950.

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investigators have been, in general, corroborated by subsequent studies. A cation exchange resin capable of neutralizing approximately 4.0 mEq. of base per gram of resin was used. In removing sodium the resin released an ion of hydrogen. A 59 year old male with hypertension and right hemiparesis was placed on a constant diet which consisted essentially of the following ingredients: sodium—112 mEq./L.*; potassium—87 mEq.; calcium—47 mEq.; inorganic phosphorus—44 mM. (milli-moles); nitrogen —11.9 gm. (representing 75 gm. of protein); water—ad lib.

The plan of study consisted of a control period of 20 days, followed by a 35 day period during which varying amounts of resin were given, and

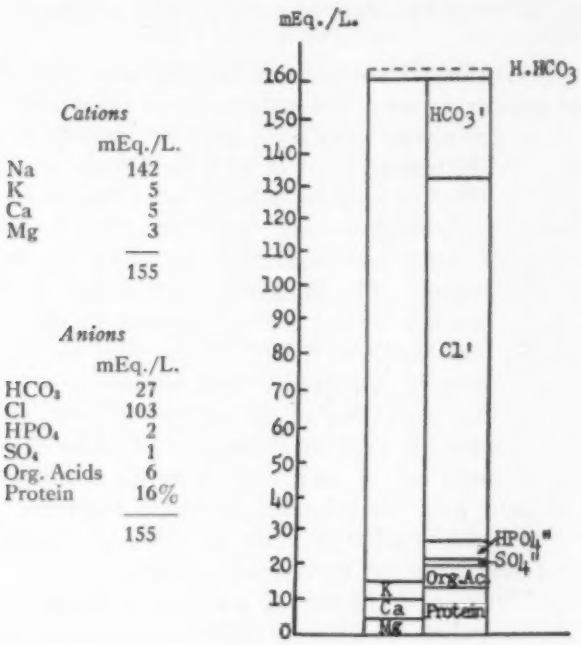

FIG. 1. Acid-base composition of blood plasma (Gamble[16])

then a period of 25 days of observation. Electrolyte studies of blood, urine and feces were made during the entire period of 80 days. During the resin administration period the quantity was increased periodically from an amount capable of neutralizing 100 mEq. of base up to 250 mEq. of base. The following observations were made: the patient remained subjectively well; he lost 3.6 kg. which was regained nine days after discontinuance of

* $\text{mEq./L.} = \frac{\text{concentration (mg./100 ml.)} \times 10 \times \text{valence}}{\text{atomic weight}}$.

Example: mEq./L. of sodium (normal plasma) $= \frac{333 \text{ mg.} \times 10 \times 1}{23} = 145$ mEq./L.

Normal values for plasma are shown in figure 1.

resin; the average urine output was 2110 c.c. per day as compared to 1640 c.c. during the control period. Fecal sodium increased from an average of 1.4 mEq. per day during the control period to an average of 51.0 mEq. per day during the resin period. This represented an excretion of approximately 80 per cent of the dietary sodium. Urinary sodium showed a marked decrease during treatment whereas plasma sodium levels remained fairly constant throughout. Studies of potassium balance showed essentially the same trend—i.e. increased fecal excretion, diminished urinary excretion, stable plasma levels. There were no changes in blood calcium levels or calcium excretion. The anions, chloride, phosphate, and sulfate, were unchanged. A moderate reduction in CO_2 combining power of the blood was noted. During the resin period, urinary ammonia levels increased to compensate for the unavailability of sodium and potassium. Nitrogen studies of the blood, urine and feces revealed no essential changes. In summary the findings indicated immobilization of sodium in the intestine and the development of a compensated metabolic acidosis.

No studies were made of variation in other electrolytes such as magnesium, iron, copper, cobalt, etc. Nor was there any study of the absorption of amino acids and vitamins. These aspects of the problem remain to be evaluated. Although hypokalemia was not observed by the authors, the possibility of a reduction in plasma potassium must be considered and guarded against. This is particularly important in view of the possible enhancement of digitalis toxicity by hypopotassemia. The increased kidney work represented by the marked increase in excreted ammonia constitutes a potential hazard in individuals with renal damage.

The two patients with congestive failure and one with cirrhosis showed similar changes in electrolyte balance. Disappearance of edema, weight loss and lessened need for mercurial diuretics were apparent. The patient with cirrhosis likewise showed diminution of edema and absorption of ascitic fluid. This patient, however, developed marked acidosis and hypopotassemia.

During 1950, seven other groups of investigators have presented data on the use of cation exchange resins in various edematous states. Chapman and Pannell [17] treated 10 patients with a resin containing potassium as the exchange ion. Electrolyte balance studies and other observations were made over a two week period. All showed improvement. None developed acidosis or potassium deficiency. Martz, Kohlstaedt and Helmer [18] treated 11 patients with heart failure and five with cirrhosis of the liver with a mixture of resins. Included in the mixture was a potassium resin designed

[16] Gamble, J. L.: Chemical anatomy, physiology and pathology of extracellular fluid, 1949, Harvard University Press.

[17] Chapman, D. W., and Pannill, C. H.: The effect of a cation exchange resin on edematous states and electrolyte balance, J. Lab. and Clin. Med. **36**: 808, 1950.

[18] Martz, B. L., Kohlstaedt, K. G., and Helmer, O. M.: The use of ion exchange resins in the management of congestive heart failure and cirrhosis of the liver, J. Lab. and Clin. Med. **36**: 962, 1950.

to prevent hypokalemia and an anion exchange resin to prevent acidosis. Sixty grams of the mixture were given per day in four doses. In every instance patients were said to prefer resin therapy to the severe dietary restrictions of a minimal sodium diet and the inconvenience of repeated injections of mercurials. Currens et al.[19] observed improvement in four patients with cardiac edema who were treated with an ammonium cation exchange resin given in doses of 30 to 120 gm./day. One patient in this group developed mild hypokalemia which was associated with generalized weakness. Danowski and his coworkers [20] employed a carboxylic cation exchange resin in its hydrogen cycle and observed electrolyte changes similar to those previously mentioned. Kahn and Emerson [21] found that by mixing equal parts of a carboxylic resin saturated with potassium and another saturated with ammonium, potassium deficiency could be avoided. One of their patients who had impairment of renal function showed no increase in urinary ammonia output and developed subclinical acidosis. They reemphasized the fact that severe renal damage is apparently a contraindication to resin therapy. Kraus [22] treated 22 patients with cardiac edema for periods of one week to three months with an ammonium resin. All showed characteristic weight loss, decrease in edema and diuresis. Potassium deficiency was observed and in four patients who were receiving digitalis signs of intoxication appeared coincidentally with the hypopotassemia. Hay and Wood [23] have recently reported essentially similar observations in a group of 10 patients.

Another clinical application of cation exchange resins has recently been reported by Elkinton and his coworkers.[24] This is concerned with the problem of potassium retention encountered in severe renal insufficiency with oliguria or anuria. The medical management of lower nephron nephrosis has been greatly improved in recent years by better understanding of the pathological physiology of the process. One of the more serious aspects of the anuric period is hyperkalemia. This has remained one of the few absolute indications for some form of artificial dialysis. When the normal value for potassium of 5 mEq./liter increases to 7.4 to 8.1 mEq./liter definite evidence of cardiotoxicity may be encountered. The methods of reducing potassium by artificial dialysis heretofore employed include the use of the

[19] Currens, J. H., Counehan, T., and Rourke, M.: Observations on the administration of ammonium cation exchange resin to patients with cardiac edema, J. Clin. Investigation **29**: 807, 1950.

[20] Danowski, T. S., Greenman, L., Mateer, F., Peters, J. H., Weigand, F. A., Mermelstein, H., and Clarke, C. E.: Carboxylic cation exchange resin studies in animals and humans, J. Clin. Investigation **29**: 807, 1950.

[21] Kahn, S. S., and Emerson, K., Jr.: Experiences with the use of cation exchange resins in the treatment of edema, J. Clin. Investigation **29**: 827, 1950.

[22] Kraus, H.: The use of a cation exchange resin in patients with cardiac edema, J. Clin. Investigation **29**: 829, 1950.

[23] Hay, S. H., and Wood, J. E.: Cation exchange resins in the treatment of congestive heart failure, Ann. Int. Med. **33**: 1139, 1950.

[24] Elkinton, J. R., Clark, J. K., Squires, R. D., Bluemle, L. W., Jr., and Crosley, A. P.: Treatment of potassium retention in anuria with cation exchange resin: a preliminary report, Am. J. M. Sc. **220**: 547, 1950.

"artificial kidney," intestinal lavage and peritoneal lavage. Elkinton and his coworkers found that the enteral (per os or per rectum) administration of an ammonium cation exchange resin would reduce potassium levels to more nearly normal values.

It will be observed from this brief survey that the clinical usefulness of ion exchange resins, although not completely established, presents the physician with a new therapeutic weapon of extraordinary versatility. Additional long term studies for detection of any evidence of chronic toxicity or the adsorption of essential metabolites are desirable. New applications await the ingenuity of chemist and clinician.

MILTON S. SACKS, M.D.

REVIEWS

Blood Clotting and Allied Problems: Transactions of the Third Conference, January 23–24, 1950, New York, N. Y. Edited by JOSEPH E. FLYNN. 224 pages; 15.5 × 23.5 cm. 1950. Josiah Macy, Jr. Foundation, New York. Price, $3.00.

Each year, the Josiah Macy, Jr. Foundation sponsors a meeting at which a small group of investigators in the general field of blood coagulation air their views and common interests. This small volume is a verbatim report of the Conference held in January 1950. Some of the material presented is highly technical and will appeal only to those who are especially concerned with blood coagulation problems. However, the discussions on vitamin K, and its use in counteracting Dicumarol effect are of more general interest. Descriptions of experimental and clinical studies with the newer anticoagulants, phenylindanedione, tromexan and paritol should interest physicians who have occasion to employ anticoagulant therapy. The book is not a review of the subject of blood coagulation, nor does it provide a complete summary of recent developments in this field. The discussion-type presentation has the advantage of making apparent the numerous differences of opinion among the clotting experts. It is to be regretted that the members of the conference do not make more use of the opportunity which these meetings provide to integrate their observations and data.

C. LOCKARD CONLEY, M.D.

Physiology of the Nervous System. 3d Ed. By JOHN FARQUHAR FULTON. 667 pages; 22.5 × 15 cm. Oxford University Press, New York. 1949. Price, $10.00.

This monograph has held a leading position in its field since the appearance of the first edition in 1938. It has filled a need hardly recognized by other authors. Written primarily from the point of view of animal experimentation it also reviews much clinical material and certain pertinent psychological studies. It represents an effort to integrate the evidence secured in these various fields into a reasonable picture of central nervous action, from the point of view of the physiologist.

In his preface the author considers the more significant new features of this edition to include (1) the discovery of secondary sensory and motor areas in the cerebral cortex; (2) the finding of inhibitory and facilitatory areas in the reticular formation, and the related observation that the suppressor areas of the cerebral cortex, as well as those of the anterior cerebellum, operate through the reticular formation; (3) the emergence of the orbital surface of the frontal lobe, the anterior cingulate gyrus and the tip of the temporal lobe as important autonomic centers; (4) the finding of discrete functional localizations in the anterior cerebellum; (5) the discovery that rhythm of stimuli determines whether the response from many excitable foci shall be excitatory or inhibitory; and (6) the recent clinical experience with frontal lobotomy.

To this list of important recent developments the reviewer may add the recent theories concerning the nature of central inhibition, in particular the views of Brooks and Eccles; the expanded discussion of autonomic regulation via the hypothalamus, especially the work of Verney on the osmoreceptors; the new work on the areas of the temporal lobe which are involved in auditory associations, and their connections with frontal and occipital lobes; and the demonstration by Bard and his associates that motion sickness ceases after localized ablation of the flocculo-nodular lobe of the cerebellum.

A radical departure in the new edition is found in the new interpretation of the rôle of acetylcholine in neuromuscular and synaptic transmission. In the second

edition the classical view of Loewi, Cannon and Dale was accepted throughout, even by Dr. David Nachmansohn, who wrote a special section on this subject. According to this view acetylcholine is a neuro-humor which diffuses across the synaptic or neuromyal gap to produce stimulation of the next cell in the chain. In the present edition the classical view appears as before on pages 229 to 231, and elsewhere, but Dr. Nachmansohn has radically revised his interpretation, on pages 70 to 92, vigorously championing the view that acetylcholine acts intracellularly, to produce electrical depolarization, but not to bridge the gap between cells. Undue space is given to this argument concerning a highly controversial subject which is not nearly as finally settled as Dr. Nachmansohn believes. Certainly many other workers in the field have not accepted his position. The recent summary by Dr. Arturo Rosenblueth * is sufficient indication that the classical view is still widely held.

Other evidences remain in the new edition that a new stratum of material has been laid down over older and still persisting textual deposits, so that consistency is not always preserved. On the whole the new material has been well integrated with the older story. In spite of some inconsistencies in interpretation, errors in statement of fact, and questionable judgment in the allocation of space, the final impression given by the new edition is one of a powerful and skillful treatment of a very difficult subject. It is a book for the experienced experimentalist or clinician, and not for the beginner. Most medical students will find it beyond their grasp, but a few determined spirits among them will discover in it a great storehouse of information, to be unlocked by earnest effort. The 1700 titles in the bibliography are the signposts directing the reader toward a dozen fascinating vistas of study.

W. R. AMBERSON

Pharmacological Basis of Penicillin Therapy. By KARL H. BEYER, Ph.D., M.D., F.A.C.P., Director, Pharmacological Research, Sharp & Dohme, Inc., Glenolden, Pa. 214 pages; 14.5 × 22.5 cm. Charles C. Thomas, Springfield, Ill. 1950. Price, $4.50.

This monograph has been prepared to present briefly the pharmacologic background that is the basis of penicillin therapy. In the first two chapters the absorption, distribution, excretion and inactivation of penicillin has been summarized and clearly presented. Chapter 3 is concerned with the mode of action of penicillin and a discussion of the two current dosage regimens in therapy. Chapter 4 is devoted to a discussion of the repository penicillin preparations. Chapters 5, 6 and 7 embrace the subject of renal elimination of penicillin. Very special consideration is given to the enzymologic basis of action of Carinamide. An addendum considers the more recently introduced benemid. The unique pharmacologic properties of the latter compound have been investigated by the author and his associates. Benemid inhibits, reversibly, the ability of the body to destroy a number of therapeutic agents by conjugation, e.g. para-aminobenzoic acid and para-aminosalicylic acid. Pertinent references are provided at the end of each chapter.

In addition to the consideration of the technical aspects of the basis of penicillin therapy, the author has presented a broad philosophy of the rôle of this antibiotic in the control of infectious diseases. Attention is called to the rather remarkable fact that the body has apparently set up almost every barrier to the admission of this useful agent to the animal organism. Further, the host uses its most effective means to rid itself of the agent once its entrance has been gained. A satisfactory explanation for these observed facts has not been made available from the scientific studies made up to this time.

* "The Transmission of Nerve Impulses at Neuroeffector Junctions and Peripheral Synapses," 1950, Technology Press and John Wiley and Sons, New York.

From the physician's standpoint it may be desirable to point out again the profound impression that this single antibiotic has made on the practice of medicine in so few years. As described by the author, some notion of the relative emphasis that the physician has placed on antibiotic therapy may be gained from the fact that in 1948 the combined sales of penicillin and streptomycin were 60 per cent of the total dollar sales of medicinals; and penicillin is not an expensive drug. Perhaps never before has a single medicinal agent made such a marked impression in so short a time period.

For those desiring a comprehensive, stimulating and authoritative review of the basis of penicillin therapy the book may be highly recommended.

C. J. C.

Differential Diagnosis of Internal Diseases. By JULIUS BAUER, M.D., F.A.C.P. 866 pages; 16 × 23.5 cm. Grune and Stratton, Inc., New York. 1950. Price, $12.00.

This excellent and scholarly compilation on diagnosis is divided into two approximately equal parts. Part one occupies the first 396 pages and deals with leading symptoms; part two, devoted to leading signs, takes up the next 417 pages.

The first part contains 12 chapters concerned in turn with headache; chest pain; abdominal pain; backache; pain in the extremities; disorders of general feelings; disorders of consciousness; vertigo, nausea and vomitus; paralysis, incoördination, and involuntary movements; cough and dyspnea; diarrhea and constipation; and hemorrhages. The second half of the book is divided into eight longer chapters dealing consecutively with the general appearance (habitus); hyperthermia, fever and infectious diseases; signs in the respiratory system, cardiovascular system, digestive system, hemopoietic system, and uropoietic system; and glycosuria. The work is completed by author and subject indexes.

This book can be highly praised. The author has combined with his individual approach to each subject in turn, an extraordinary display of knowledge. In fact one is reminded of the village master and wonders likewise at Dr. Bauer "that one small head could carry all he knew." There is a wealth of detailed information included in this volume, new and old, American and European. Dr. Bauer was formerly Professor of Medicine in the University of Vienna, and there can be few living men who enjoy such evident familiarity with the medical literature of both continents. A total of nearly 1500 references document the text.

The only flaws detected are minor, as, for example, the rather poor description of pulsus alternans on page 577 which tends to confuse it with pulsus bigeminus. Some of the rarer causes of hypertension are not mentioned, and indeed, some sections appear to be written with greater authority and knowledge than others. This is not unnatural and on the whole the text more than adequately covers the differential diagnosis of all the common symptoms and signs encountered in the practice of internal medicine. The author uses "the latter" which is a facile enough device for the writer, but it is invariably an irritating brake to the reader and should never be used in expository writing. Illustrations are limited to about 50, but they are all of high standard and each serves a useful purpose.

The author emphasizes that diagnosis is the beginning and the end of internal medicine, and that every internist must be a "minor psychiatrist"; he deplores the superfluous use of laboratory investigations which, when indulged to excess, he describes picturesquely as "preposterous outgrowths of mechanized medicine." These healthy attitudes pervade the well written text, which is amply illustrated with numerous case reports.

This book is an education to read and will remain an invaluable work of reference.

H. J. L. M.

Facts About the Menopause. By MAXINE DAVIS. 172 pages; 14 × 21 cm. McGraw-Hill Book Co., Inc., N. Y. 1951. Price, $2.50.

According to the author "this volume has been written for the many women who have asked me for complete information about the change of life. I hope that I can demonstrate that there is nothing to fear. I trust I shall be able to prove conclusively that the middle years are indeed the best years of our lives."

The book is in two parts: Part 1 dealing with facts about the change of life covers a wide range of subjects from "It Is Your Glands" to "Men Go through It Too." It is filled with medical terms followed by short definitions and explanations. A lay reader would most certainly be stimulated to ask questions and more questions before reaching a complete understanding of the subject. Physicians, whose patients read this book, will wish that the author had not given such definite methods of treatment, examinations, etc., which, in some instances, are no longer considered the most effective.

Part 2: "Facts for the Forties" is well written, easily read, practical and full of common sense. One feels that the author has come out of the depths of medical terminology and is again on familiar ground. The final chapter in which the woman past 40 is given understanding, and encouraged to face the future calmly and unafraid is well worth reading.

M. B. B.

Methods in Medical Research. Volumes 2 and 3. JULIUS H. COMROE, JR., Editor-in-Chief, Volume 2; RALPH W. GERARD, Editor-in-Chief, Volume 3. 361 pages; 14 × 22.5 cm. The Year Book Publishers, Inc., Chicago. 1950. Price, Volume 2, $6.50; Volume 3, $7.00.

These volumes continue the same high standard of quality which characterized the opening volume. As in it, the material consists of detailed methodology including critical and comparative comments and discussions of principles.

Volume 2, edited by Julius H. Comroe, Jr., consists of sections on three very different subjects: I. Methods of Study of Bacterial Viruses. II. Pulmonary Function Tests. III. Assay of Hormone Secretions. These sections are edited by M. H. Adams, J. H. Comroe, Jr., and E. H. Venning, respectively. The sections are subdivided into short chapters written by these editors and other authorities on the particular methods.

Volume 3 is edited by R. W. Gerard. The sections are: I. Genetics of Micro-Organisms. II. Assay of Neurohumors. III. Selected Psychomotor Measurement Methods. IV. Methods for Study of Peptide Structure. The sections are edited by S. E. Luria, J. H. Gaddum, W. R. Miles and C. H. Li, respectively. These reference books are highly valuable to investigators concerned with the particular subjects treated.

G. E. G.

Color Atlas of Pathology. Prepared under the auspices of the U. S. Naval Medical School of the National Naval Medical Center, Bethesda, Maryland. Illustrated by 1053 figures in color on 365 plates. Published by J. B. Lippincott Company, East Washington Square, Philadelphia, Pa. 1950. Price, $20.00.

This book covers diseases of the hematopoietic system, the reticuloendothelial system, the respiratory tract, the cardiovascular system, the liver, the alimentary tract, the kidney and urinary tract and the musculo-skeletal system. There is a brief discussion of the diseases affecting the various systems at the beginning of each section. Short histories of the illustrated cases are presented. The illustrations are

excellent. Most of them are photomicrographs but pertinent roentgenographs and photographs of gross specimens are presented.

The book is to be recommended to teachers of pathology, to pathologists and to medical students as an aid to the study of histopathology. It deserves commendation but its use should not preclude the exercise derived from study of actual pathologic material and traditional texts.

H. R. S.

BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Anatomy of the Nervous System. 2nd Ed. By OLOF LARSELL, M.A., Ph.D., Sc.D., Professor of Anatomy, University of Oregon Medical School, Portland; Introduction by A. T. RASMUSSEN, Ph.D. 520 pages; 25.5 × 17 cm. 1951. Appleton-Century-Crofts, Inc., New York. Price, $9.00.

British Medical Bulletin. Part I: Industrial Hazards; Part II: Commentary—History—Documentation. Volume 7, Number 1–2, 1950. 144 pages; 28 × 22 cm. (paper-bound). 1951. Published by Medical Department, The British Council, an agent of the British Government; obtainable in U. S. A. from Oxford University Press, New York. Price, $2.00.

Paul Ehrlich. By MARTHA MARQUARDT; with an Introduction by SIR HENRY DALE. 255 pages; 21.5 × 14 cm. 1951. Henry Schuman, New York. Price, $3.50.

Facts About the Menopause. By MAXINE DAVIS. 172 pages; 21 × 14 cm. 1951. McGraw-Hill Book Company, Inc., New York. Price, $2.50.

Good Food for Diabetics. By ELEANOR RECORD SIGEL. 144 pages; 20 × 13.5 cm. 1951. Harper & Brothers, New York. Price, $2.50.

Health and Disease in the Tropics. By CHARLES WILCOCKS, M.D., F.R.C.P., D.T.M.&H., Director, Bureau of Hygiene and Tropical Diseases, etc.; illustrated by JOHN HULL GRUNDY and the AUTHOR. 200 pages; 22 × 14.5 cm. 1951. Oxford University Press, New York. Price, $3.25.

Introduction to Surgery. By VIRGINIA KNEELAND FRANTZ, M.D., Associate Professor of Surgery, College of Physicians and Surgeons, Columbia University, etc., and HAROLD DORTIC HARVEY, M.D., Assistant Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University, etc. 233 pages; 19 × 12.5 cm. 1951. Oxford University Press, New York. Price, $2.75.

Klinische Chemie und Mikroskopie. Ausgewählte Untersuchungsmethoden für das medizinisch-chemische Laboratorium. By DR. LOTHAR HALLMANN. 594 pages; 21 × 15 cm. 1950. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, $5.85.

James Lind, Founder of Nautical Medicine. By LOUIS H. RODDIS, Captain, Medical Corps, U. S. Navy. 177 pages; 21.5 × 14 cm. 1951. Henry Schuman, New York. Price, $3.00.

The Management of the Patient with Severe Bronchial Asthma. By MAURICE S. SEGAL, M.D., Assistant Professor in Medicine, Tufts College Medical School, etc. 158 pages; 22.5 × 14 cm. 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $3.50.

Nasal Sinuses: An Anatomic and Clinical Consideration. 2nd Ed. By O. E. VAN ALYEA, M.D., Associate Clinical Professor, Department of Laryngology, Rhinology, and Otology, University of Illinois College of Medicine, Chicago. 327 pages; 23.5 × 15.5 cm. 1951. The Williams & Wilkins Company, Baltimore. Price, $9.00.

Parasitic Infections in Man: Symposium Held at the New York Academy of Medicine, March 15 and 16, 1949. Edited by HARRY MOST. 229 pages; 23.5 × 15.5 cm. 1951. Columbia University Press, New York. Price, $4.50.

Principles and Practice of Bacteriology. 4th Ed. (College Outline Series.) By ARTHUR H. BRYAN, University of Baltimore, etc., and CHARLES G. BRYAN, Porth and Llwympia Hospitals, England. 410 pages; 21 × 13.5 cm. (paper-bound). 1951. Barnes & Noble, Inc., New York. Price, $1.75.

Die Staublungenerkrankungen. By o. ö. PROF. DR. K. W. JÖTTEN and PROF. DR. H. GÄRTNER. 336 pages; 23 × 15.5 cm. (paper-bound). 1950. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, DM 20,—geb. DM 22, –.

A Textbook of the Practice of Medicine. 8th Ed. By VARIOUS AUTHORS; Edited by FREDERICK W. PRICE, F.R.S.Ed., M.D., C.M.Ed., F.R.C.P.Lond., Hon.M.D. Belf, Consulting Physician to the Royal Northern Hospital and to the National Hospital for Diseases of the Heart, London, etc. 2076 pages; 22.5 × 14.5 cm. 1951. Oxford University Press, New York. Price, $9.00.

Verhandlungen der deutschen Gesellschaft für Kreislaufforschung. By PROF. DR. HANS SCHAEFER. 274 pages; 23 × 15.5 cm. (paper-bound). 1950. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, DM 26.—, geb. DM.

Virus and Rickettsial Diseases. By S. P. BEDSON, M.D., F.R.C.P., F.R.S., Professor of Bacteriology, London Hospital; A. W. DOWNIE, D.Sc., M.D., Professor of Bacteriology, University of Liverpool; F. O. MACCALLUM, B.Sc., M.D., Director Virus Laboratory, Central Public Health Laboratory, and C. H. STUART-HARRIS, M.D., F.R.C.P., Professor of Medicine, University of Sheffield. 383 pages; 22 × 14 cm. 1950. The Williams & Wilkins Company, Baltimore. Price, $4.50.

Zur Frage der Cortison-Wirkung (Die "Corticogene Kettenreaktion"). By PROF. DR. W. BEIGLBÖCK, DR. H. HOFF and MED. R. CLOTTEN. 142 pages; 24 × 17 cm. 1950. Dr. med. Hans Hoffe, Augsberg, Bavaria, Germany. Price, kart DM 6.50.

COLLEGE NEWS NOTES

American College of Physicians to Publish New Directory

During the summer and early autumn a new and revised Directory of the College will be published. Immediately after the 1951 Annual Session in St. Louis in April, the editors will begin work by submitting to every member his last published biographical data for revision. It is anticipated that the new Directory will exceed 800 pages in volume and will cost $14,000 approximately. The Board of Regents has provided that the College will absorb a portion of the cost, charging members who file their orders in advance only $4.00 per copy. To others the subscription rate for the Directory will probably be $6.00, depending on the final cost. Order forms to members will accompany the request for revision of copy.

New Life Members—The American College of Physicians

The College is gratified to announce that the following Fellows have become Life Members of the American College of Physicians, since the publication of the last issue of this journal:

John Boyer Levan, Reading, Pa.
Francis Leo Foran, Chicago, Ill.
Emile Gordon Stoloff, New York, N. Y.
Chauncey Angus McKinlay, Minneapolis, Minn.
Carll Seymour Mundy, Toledo, Ohio

American Board of Nutrition

Recently the American Board of Nutrition was organized "to establish standards of qualification of persons as specialists in the field of human nutrition and to certify as such, persons who comply with the standards so established." The Board is analogous in purpose, function and organization to the various medical specialty boards which have served for many years to establish standards and qualifications for persons wishing to practice in a specialized field of medicine. Those concerned with establishment of this Board include representatives from the American Institute of Nutrition, American Medical Association, American Public Health Association, American Society of Biological Chemists, and the Association of American Medical Colleges. Dr. John B. Youmans, F.A.C.P., Nashville, Tenn., is President, and Dr. Otto A. Bessey of the University of Illinois College of Medicine, Chicago, is the Secretary-Treasurer.

Qualifications for certification include:

(a) Citizenship of the United States or Canada.
(b) Presentation of evidence of satisfactory moral and ethical standing.
(c) Ph.D. degree in a biological science, or M.D. degree from an approved school.
(d) Courses or training equivalent to a minimum of three semester hours in at least three of the following five subjects: food technology, microbiology of food, human physiology, large-scale food preparation and hospital dietetics.
(e) Three years' experience in the practical aspects of human nutrition.
(f) Pass written and oral examinations provided by the Board and designed to test the applicant's knowledge of the biological sciences concerned with nutrition and the application of such knowledge to the practical aspects of human nutrition.

(g) Until July 1, 1951, candidates may be certified on the basis of their training and experience, with satisfactory experience in lieu of formal courses in the subjects listed under item "d" without examination. After that date all applicants will be required to submit to examination.

A certificate granted by the Board does not of itself confer or purport to confer any degree, legal qualification, privileges, or license. The aim of the Board is to improve the standards of the practice of the science of human nutrition and to certify as specialists those who voluntarily comply with the requirements and regulations of the Board. Application must be made in triplicate on the special form provided and must be complete, including letters, etc., before it can be considered. A fee of $35.00 must accompany the application.

American Board of Pediatrics

The following is the schedule of oral examinations to be held by the American Board of Pediatrics:

Atlantic City, N. J.—May 5, 6 and 7, 1951.
Detroit, Mich.—June 8, 9 and 10, 1951.

The examination in Detroit replaces the one originally scheduled for Cleveland, Ohio, in June.

American Academy of Allergy Offers Postgraduate Course

A postgraduate course in Allergy will be offered by the American Academy of Allergy at Montreal, Canada, June 14–15–16, 1951. The course is being given with the coöperation of the McGill University Faculty of Medicine and the classes will meet at the Royal Victoria Hospital. The registration fee is $50.00. Information, registration forms and outlines of the course may be obtained from Bram Rose, M.D., Royal Victoria Hospital, Montreal 2, Canada.

Michael Reese Hospital Postgraduate School, Chicago, Announces Courses for Spring and Summer 1951

Dr. Samuel Soskin, F.A.C.P., Dean of the Michael Reese Hospital Postgraduate School, announces the following courses, which are intended primarily for physicians in general practice who wish to keep abreast of current trends in the various specialist phases of medicine.

CLINICAL DERMATOLOGY—April 2–6; tuition, $50.00.

SURGERY—Indications, Pre- and Post-Operative Care, April 9–14; tuition, $50.00.

RECENT ADVANCES IN INTERNAL MEDICINE, April 20–May 12; tuition, $100.00.

RECENT ADVANCES IN PEDIATRICS, May 21–26; tuition, $50.00.

DISEASES OF THE ENDOCRINES, July 9–21; tuition, $100.00.

HEMATOLOGIC DIAGNOSIS, July 23–August 4.

The American Association of the History of Medicine will hold its annual meeting in Baltimore, Md., at the Institute of the History of Medicine of Johns Hopkins University, May 3–5, 1951. Further details may be obtained by addressing the Secretary of the Association, Dr. Iago Galdston, 2 E. 103rd St., New York 21, N. Y.

The American Goiter Association will hold its annual meeting in Columbus, Ohio, May 24–26, 1951. The program will consist of papers dealing with goiter and other diseases of the thyroid gland, dry clinics and demonstrations.

The International Congress of Physical Medicine, organized by the British Board of Management of the International Federation of Physical Medicine, will be held in London, England, July 14–19, 1952. A complete scientific program is being prepared, and applications for the provisional program should be addressed to the Honorary Secretary, International Congress of Physical Medicine (1952), 45 Lincoln's Inn Fields, London, W.C.2, England.

The Second International Gerontological Congress will be held in St. Louis, Mo., September 9–14, 1951. Sponsors of this Congress, which have the approval of the Council for the Coördination of International Congresses of Medical Sciences, are The International Association of Gerontological Societies, The Gerontological Society, Inc., and The American Geriatrics Society. The American College of Physicians is one of the coöperating organizations. Further details may be obtained by writing Dr. E. V. Cowdry, Washington University School of Medicine, St. Louis 10, Mo.

The dedication ceremonies for Ohio's new Health Center, located on the campus of the Ohio State University, will be held in the Health Center Quadrangle, May 14–16, 1951. New buildings to be dedicated are the 600-bed University Hospital, the College of Dentistry building, the 300-bed Tuberculosis Hospital, and the 140-bed Receiving Hospital for mental patients.

The annual Winston-Salem Memorial Heart Symposium and Clinics were held April 12–13 at the Bowman Gray School of Medicine of Wake Forest College under the sponsorship of the Winston-Salem Heart Association. Dr. Robert L. McMillan, F.A.C.P., of the Bowman Gray School of Medicine of Wake Forest College, was in charge of arrangements. Included among the participants were the following Fellows of the College: Dr. R. Bruce Logue, Atlanta, Ga.; Dr. Louis N. Katz, Chicago, Ill.; Dr. E. Sterling Nichol, Miami, Fla.; Dr. A. Carlton Ernstene, Cleveland, Ohio; and Dr. Edward Weiss, Philadelphia, Pa.

10th Annual Walter L. Niles Memorial Lecture

Dr. Eugene A. Stead, Jr., F.A.C.P., Professor of Medicine at Duke University School of Medicine and Physician-in-Chief to the Duke Hospital, Durham, N. C., delivered the 10th Annual Walter L. Niles Memorial Lecture at Cornell University Medical College at 8:00 p.m. on Friday evening, April 20. Dr. Stead's title was "Congestive Heart Failure."

The Walter L. Niles Memorial Lecture, sponsored by the Nu Sigma Nu medical fraternity, is delivered each year at Cornell University Medical College in memory of Dr. Niles, former Professor of Clinical Medicine and Dean of the Medical College. In the past the lecture has been delivered by such prominent physicians as Dr. W. Barry Wood, F.A.C.P., St. Louis, Mo., Dr. William Menninger, F.A.C.P., Topeka, Kans., Dr. Chester S. Keefer, F.A.C.P., Boston, Mass., Dr. Allen Whipple, New York, N. Y., and by Dr. Edward Strecker, F.A.C.P., Philadelphia, Pa.

Dr. Charles H. Lutterloh, F.A.C.P., formerly of Hot Springs National Park, Ark., recently assumed the position of Assistant Chief of Professional Services at the Veterans Administration Hospital, Little Rock, Ark.

Among the speakers who participated in the second symposium on "Clinical Problems of Advancing Years," which was held on March 15 in Philadelphia under the sponsorship of Smith, Kline & French Laboratories were: Dr. George W. Thorn, F.A.C.P., Boston, Mass., "Studies on ACTH and Cortisone"; Dr. David P. Barr, F.A.C.P., New York, N. Y., "Relationship of Endocrine Factors to Development of Diabetes Mellitus"; Dr. Tinsley R. Harrison, F.A.C.P., Birmingham, Ala., "Load and Age in Regard to Myocardial Failure"; Dr. Walter C. Alvarez, F.A.C.P., "The Little Strokes."

A feature of the symposium was a color television program presented from the Wills Hospital, Philadelphia. Dr. George Morris Piersol, M.A.C.P., Philadelphia, presented a medical clinic, "Rehabilitation of the Physically Handicapped," and Dr. Kendall A. Elsom, F.A.C.P., Philadelphia, spoke on "The Rôle of Color Television in Medical Teaching."

Dr. M. Coleman Harris, F.A.C.P., was recently elected President of the Los Angeles Society of Allergy. Dr. Harris is also Secretary of the Allergy Section of the California Medical Association, and Secretary and Treasurer of the California Society of Allergy.

Dr. Howard A. Rusk, F.A.C.P., Director of the Institute of Rehabilitation and Physical Medicine of the New York University-Bellevue Medical Center, was awarded the 1951 Research Award of the American Pharmaceutical Manufacturers Association. Dr. Rusk was the first clinician to receive this award which was presented at the Annual Session of the A.P.M.A. at Boca Raton, Fla., on April 2. In announcing this award, Dr. Martin Lasersohn, Chairman of the Research Board and Vice President of Winthrop-Stearns, Inc., said, "Dr. Rusk's research has been directly responsible for the rehabilitation to active useful life of many thousands of servicemen who sustained catastrophic injury and crippling, as well as civilians handicapped from accidents and from such paralyzing diseases as poliomyelitis, multiple sclerosis, apoplexy and cerebral palsy."

Dr. John H. Talbot, F.A.C.P., Buffalo, N. Y., is a member of a five-man team of Army military and civilian experts in the field of cold weather injuries, which is now in Japan and Korea studying frostbite cases, with a view toward improving methods of preventing and treating this type of injury. The team's twofold mission, according to Major General R. W. Bliss, Surgeon General, U. S. Army, is to study and evaluate the Army's present program for the prevention and treatment of cold injuries and to recommend the best methods of treatment to be followed in the medical care of cold casualties.

Dr. Lyle J. Roberts, F.A.C.P., who retired from the Medical Corps, U. S. Navy, on January 1 with the rank of Captain, has been named Health Officer for District 6, West Virginia, with headquarters at Martinsburg.

Dr. Hans Popper, F.A.C.P., Associate Professor of Pathology at Northwestern University Medical School and Director of the Pathological Laboratories at Cook County Hospital, has been appointed to the editorial board of *Gastroenterology*.

Dr. Philip S. Hench, F.A.C.P., and Dr. Edward C. Kendall, of the Mayo Clinic, Rochester, Minn., were presented with an Award of Merit by the Masonic Foundation for Medical Research and Human Welfare on February 15, for their contribution to the study of rheumatic fever. The ceremony was part of a two-day conference on progress made in studies by six medical research units working over the past three years on rheumatoid diseases under grants from the Grand Lodge, Free and Accepted Masons of New York State.

At the annual election of officers on January 23, the New York Tuberculosis and Health Association elected Dr. Foster Murray, F.A.C.P., Brooklyn, Vice President, and Dr. Anthony J. Lanza, F.A.C.P., New York, Secretary.

Dr. Albert Salisbury Hyman, F.A.C.P., New York, N. Y., Associate Professor of Clinical Medicine at New York Medical College, Flower and Fifth Avenue Hospitals, has been appointed Consulting Cardiologist to the new Valley Forge National Heart Institute and Hospital and Director of Clinical Research at the Institute under the Leeds-Murray Foundation. Dr. Hyman's new book for the laity, *For Whom the Bell Tinkles; Heart Disease Conquered,* will be published during the summer of 1951. The title is from one of Cabot's little known aphorisms which runs: "Lucky is the man for whom the bell tinkles before it tolls."

Dr. Sara M. Jordan, F.A.C.P., Director of Gastro-enterology at the Lahey Clinic, Boston, Mass., was one of five women physicians awarded Elizabeth Blackwell citations on January 28 for their contributions to the practice and teaching of medicine.

The Blackwell awards were established in 1949 to commemorate the one hundredth anniversary of the graduation of Dr. Elizabeth Blackwell, the first woman to receive a medical degree in America.

Among the speakers at the Second Michigan Industrial Health Day program, held on April 4 in Detroit, were Dr. Robert C. Page, F.A.C.P., New York, N. Y., "International Industrial Medicine"; Dr. Oscar A. Sander, F.A.C.P., Milwaukee, Wis., "Beryllium Poisoning"; Dr. Charles L. Dunham (Associate), Washington, D. C., "Management of Injuries"; and Alfred W. Pennington (Associate), Wilmington, Del., "The Rising Toll of Obesity in Industry."

Dr. Edward P. Cawley (Associate), Assistant Professor of Dermatology and Syphilology at the University of Michigan Medical School, has been appointed Professor and Chairman of the Department of Dermatology and Syphilology at the University of Virginia Department of Medicine. Dr. Cawley succeeds Dr. Dudley C. Smith, F.A.C.P., who died August 30, 1950.

The guest speakers at the annual Spring Clinical Conference of the Dallas Southern Clinical Society, held March 26–29 in Dallas, included Dr. Dickinson W. Richards, Jr., F.A.C.P., New York, N. Y., "Mechanics of Respiration, Normal and Abnormal"; Dr. Francis E. Senear, F.A.C.P., Chicago, Ill., "Acute Disseminated Lupus Erythematosus"; and Dr. William A. Sodeman, F.A.C.P., New Orleans, La., "Tobacco and the Circulation."

The Wisconsin Trudeau Society convened at Marquette University on March 31 in connection with a postgraduate course in pulmonary diseases. Among the guest speakers were Dr. H. McLeod Riggins, F.A.C.P., New York, N. Y., "Studies on Pathologic Physiology of Tuberculous Cavities"; Dr. David T. Smith, F.A.C.P., Durham, N. C., "Moniliasis and Its Treatment"; and Dr. Richard V. Ebert (Associate), Minneapolis, Minn., "Emphysema."

Dr. Maxwell M. Wintrobe, F.A.C.P., Salt Lake City, was one of the moderators for the Fourth Utah Cancer Symposium held March 1–2 in Salt Lake City.

OBITUARIES

DR. T. HOMER COFFEN

Thomas Homer Coffen, B.S., M.S., M.D., F.A.C.P., of Portland, Ore., was born in Minneapolis, Minn., in 1877, and died January 9, 1951, of carcinoma of the stomach.

He received his academic degrees from the University of Pennsylvania, and his M.D. degree from Johns Hopkins University School of Medicine in 1906. Dr. Coffen's postgraduate training included work at the New York University Post-Graduate Medical School from 1906 to 1913. He also studied in Europe during 1913, taking short courses in Berlin, Vienna and Paris.

Following his postgraduate studies, Dr. Coffen came to Portland and entered the private practice of Internal Medicine. He was one of the pioneers of this specialty in this city, and during his lifetime enjoyed a most distinguished career.

Dr. Coffen early associated himself with medical teaching, became Assistant Professor of Medicine at the University of Oregon Medical School in 1913 and was appointed Clinical Professor of Medicine in 1924, a position which he held until he was named Professor Emeritus of Medicine in 1949. He was on the staffs of St. Vincent's and Good Samaritan Hospitals.

Dr. Coffen was a masterful clinician and a fine teacher. His work was largely confined to cardiology. His interest in students and internes was profound, and he went to great lengths, at a time when facilities were scant, to bring to the student and the hospital staff the most modern thinking in his field.

Dr. Coffen held numerous offices in various medical societies and was Treasurer of the American Heart Association in 1941. He was a Diplomate of the American Board of Internal Medicine. Dr. Coffen was elected a Fellow of the American College of Physicians in 1921 and became a Life Member in 1948. He was particularly active in the College and served as Governor for Oregon from 1931 to 1940. In 1940 he was elected to the Board of Regents and served in this capacity until 1946. He was then elected Third Vice President of the College for the years 1946–47.

Many young physicians will remember Dr. Coffen's sincere interest in their progress while he was still active in teaching and College affairs. He had the faculty of being one of them and never missed an opportunity to encourage and boost the young doctor who was making his beginning in Medicine.

Dr. Coffen contributed much to his community and enjoyed wide respect and acquaintanceship all over the Northwest. Even in the last years of his life his interest in medicine, his patients and his friends never flagged. He will be long and fondly remembered by a host of people in the Northwest.

HOWARD P. LEWIS, M.D., F.A.C.P.,
Governor for Oregon

DR. JOSEPH EDWARD BRADY

Dr. Joseph Edward Brady, of Brockton, Mass., was born in 1880, and died on August 28, 1950. Dr. Brady was a graduate of Yale University School of Medicine in 1906 and soon thereafter began the practice of medicine in Brockton, where he remained active until his death. During the early part of his medical life he became interested in pediatrics and was a member of the Pediatric Service for a period of four years at the Brockton Hospital, before devoting most of his time to internal medicine. For many years he was the physician-in-chief of the Allergy Clinic and a member of the staff of the Brockton Hospital. His loyalty was rewarded by election to the office of President of the Staff. He was elected as an Associate of the American College of Physicians, February 24, 1926.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts

DR. LEON STUART GORDON

Dr. Leon Stuart Gordon, F.A.C.P., Washington, D. C., died on July 24, 1950, of a cerebral hemorrhage.

He was born in Baltimore, Md., August 4, 1904; received his M.D., 1928, A.B., 1929, A.M., 1930, and Ph.D., 1932, from George Washington University; he pursued postgraduate work in internal medicine at the University of Pennsylvania Graduate School of Medicine in 1932–33; he served as Assistant Professor of Pathology, 1929–32, at George Washington University School of Medicine.

Dr. Gordon was a member of the Attending Staff of Doctors Hospital, of the Courtesy Staff of the Central Dispensary and Emergency Hospital and the George Washington University Hospital. He was a former Vice President of the Jacobi Medical Society, a member of the District of Columbia Medical Society, a Fellow of the American Medical Association, a Diplomate of the National Board of Medical Examiners, was certified by the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1941.

DR. ROBERT URIE PATTERSON

Robert Urie Patterson, M.D., C.M., LL.D., F.A.C.P., was born in Montreal, Que., Canada, on June 16, 1877. He was a graduate of McGill University Faculty of Medicine, M.D., C.M., 1898; was awarded the LL.D. by McGill University in 1932; and was an honor graduate of the U. S. Army Medical School in 1902. Although Dr. Patterson was born in Montreal, his parents were citizens of the United States and he spent his youth in San Antonio, Tex. He returned to Montreal for his medical education.

He was appointed First Lieutenant in the Medical Corps, U. S. Army, in June, 1901, served with distinction during the Moro insurrection in the Philippines and was awarded two Silver Star Medals for "gallantry in action." As a Colonel during World War I, he served with a base hospital in Europe and was a member of the

American Military Mission in Italy. He was awarded the Distinguished Service Medal for his war work. He became Surgeon General, U. S. Army, with the rank of Major General in June, 1931, and served in this capacity until his retirement from the Army in May, 1935.

In 1935 Dr. Patterson became Dean of the University of Oklahoma School of Medicine, and also Superintendent of the University Hospitals, Oklahoma City. In 1942 he was appointed Dean of the University of Maryland School of Medicine and he held this position until June, 1946, when he retired.

Dr. Patterson was elected a Fellow of the American College of Surgeons in 1916, and was elected a Fellow of the American College of Physicians in 1931. By virtue of his rank as Surgeon General, he was elected College Governor for the Medical Corps, U. S. Army, and held this office until his military retirement in 1935.

Dr. Patterson was the author of numerous articles appearing in medical journals, principally on medico-military subjects. He was a member of Phi Beta Kappa and Alpha Omega Alpha, and was a 32nd degree Mason.

On the morning of December 6, 1950, Dr. Patterson was taken to Walter Reed General Hospital and died the same day of pneumonia. In the passing of Dr. Patterson the College lost a stalwart member, and the University of Maryland School of Medicine a friend, counselor, and able advisor.

WETHERBEE FORT, M.D., F.A.C.P.,
Governor for Maryland

DR. PAUL ALLISON YODER

Dr. Paul Allison Yoder, F.A.C.P., literally died in harness, on February 12, 1951. Although he had been forced by a previous illness to resign as Superintendent of the Forsyth County Tuberculosis Sanatorium, he continued to serve in an advisory capacity, and to the very end gave too generously of his strength and professional skill in helping carry on the work of the institution. He was examining a patient when the final summons came, in the form of a cerebral accident which was mercifully quick and painless.

Dr. Yoder was born in Hickory, N. C., March 9, 1895; was graduated with the A.B. degree from Lenoir College in 1916; served in World War I from October, 1917, to January, 1919; was graduated from the University of Pennsylvania School of Medicine in 1923, having taken his first two years in medicine at the University of North Carolina; was intern at Bryn Mawr Hospital, 1923–1924; was Staff Physician at the North Carolina Sanatorium from 1924 to 1929; and was Superintendent and Medical Director of the Forsyth County Sanatorium from its beginning in November, 1929, until December, 1949. He was Secretary of the Forsyth County Medical Society from 1934 to 1942, and President in 1947. He was a member of the North Carolina Medical Society, the American Medical Association, the Southern Medical Association, the North Carolina Tuberculosis Association (President, 1938–1940), and the National Tuberculosis Association. Since 1936 he has been a Fellow of the American College of Physicians.

The list of Dr. Yoder's achievements attests to his professional ability, but does not begin to tell of Paul Yoder, the warm, lovable man that his friends and his patients knew him to be. Indeed, his patients were his friends, as were countless relatives of his patients. He worked far longer hours than were demanded by his job, and did many things beyond the call of duty. Patients were never mere cases to him, but human beings who were sick and who needed help; and he never considered his own comfort or convenience when he had an opportunity to render service.

In 1926 he married Miss Evelyn Dale, who was a nurse in training when he

was an intern at Bryn Mawr. She was a real helpmeet in every sense of the word. Together they made the Forsyth County Sanatorium a haven of refuge.

When the two-year medical school of Wake Forest College was expanded into the Bowman Gray School of Medicine and moved to Winston-Salem in 1941, Dr. Yoder was made an Assistant Professor of Clinical Medicine. Since he was a born teacher, it required no unusual effort on his part to take an active part in teaching students and house officers. A former house officer of the North Carolina Baptist Hospital expressed the feeling of all these young men when he wrote in a letter to the *Winston-Salem Journal:* "Those former members of the Baptist Hospital house-staff and the former students at Bowman Gray School of Medicine who entertained the good fortune to work with Dr. Yoder will never forget the eager enthusiasm with which he employed his fluoroscopic screen. It has been said many times by his professional associates that Dr. Yoder could see more with a dimly illuminated fluoroscope than many chest experts could with a full sized x-ray film."

This young man chose his words when he referred to the doctors who *worked with him,* and not who *worked for him.* I doubt that any assistant ever did other than work with him, because that is the way Dr. Yoder worked. He was a teacher and a scholar in the true sense of the word, and demonstrated this with his attempts to impart to all who sought to learn, student, doctor, and patient alike.

As the *Winston-Salem Journal* commented editorially: "Dr. Yoder will continue to live in the lives of the many former tuberculosis patients he has helped restore to health, and his influence will be felt in the thousands of other lives which have benefited indirectly from his work, his research, study and writings."

WINGATE M. JOHNSON, M.D., F.A.C.P.

DR. LEON ALBERT GOLDSMITH

Leon Albert Goldsmith, A.B., M.D., F.A.C.P., of Portland, Ore., was born on November 6, 1896, and died November 2, 1950, of coronary heart disease. In 1918 he received his A.B. degree from Reed College, and in 1922 he received his M.D. degree from Harvard Medical School. He had been a member of the faculty of the University of Oregon Medical School since 1925, advancing to Assistant Clinical Professor of Medicine. He was a member of the Multnomah County Medical Society, the Oregon State Medical Society, the Portland Academy of Medicine, and the North Pacific Society of Internal Medicine. He was a Fellow of the American Medical Association and a Diplomate of the American Board of Internal Medicine. In 1936 he was elected a Fellow of the American College of Physicians.

Dr. Goldsmith had a large private practice, but found time for long, distinguished effort in medical teaching and civic affairs. He was one of the group who established the Cardiology Clinic at the University of Oregon Medical School. His enthusiasm and fine teaching ability will be long remembered by his many former students.

His civic activities included the office of Medical Director of the State Welfare Commission. His sound judgment and energy contributed greatly to the smoothness of operation of this important department. One of his abiding interests was Reed College, his alma mater, which he served as Regent for over 10 years.

During the last years of his life, Dr. Goldsmith devoted much study and time to the problem of rehabilitation of patients suffering from cardiac disease. The impact of his efforts in this direction was felt all over the state.

Dr. Goldsmith had a host of friends in and out of the medical profession. Always a friend of the young physician, his memory will linger long in this community.

HOWARD P. LEWIS, M.D., F.A.C.P.,
Governor for Oregon

DR. JAMES FRANCIS ROONEY

James Francis Rooney, M.D., F.A.C.P., died in Albany, N. Y., on February 4, 1951, from arteriosclerotic heart disease. He was 72 years of age. Dr. Rooney received his academic degree from St. John's University in 1895, and his M.D. from Union University Medical Department (now Albany Medical College) in 1898. He also did postgraduate work in pathology in Munich, Berlin, Strassburg and Vienna in 1898.

Between 1908 and 1914 he was identified with the Medical Clinic at the Albany Hospital and at one time he served as Chief of the Medical Clinic. For many years he was Attending Physician at St. Peter's Hospital in Albany, N. Y., and was Chief of Medicine from 1949 to 1951. Dr. Rooney was consultant in Medicine for years at Memorial Hospital of Greene County, Catskill, and Moses-Ludington Hospital, Ticonderoga, N. Y.

In 1921–1922, Dr. Rooney was president of the Medical Society of the State of New York, and in 1927 was elected to its Board of Trustees, which he served as Chairman in 1931–1932, 1936–1937, and 1946–1947. He had been a director of the Veterans Medical Service Plan of New York since its inception in 1946 and chairman of the State Society's War Memorial Committee since its organization in 1947. An advisor on the procurement of medical men for the armed forces during two wars, Dr. Rooney was Chairman of the Advisory Committee for Selective Service for Medical, Dental and allied specialists. During World War I, he headed the medical division in the State's procurement organization, receiving the Conspicuous Service Cross for his work. Called to active Army duty in 1941, Dr. Rooney served as Executive Officer of the 134th Medical Regiment of the Twenty-Seventh Division.

Dr. Rooney became a Fellow of the American College of Physicians in 1916, and was one of its earliest members and had a very active interest in the College. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American Medical Association. He was also a member of the New York Academy of Medicine, the Albany County Medical Society, and the Medical Society of the State of New York.

Dr. Rooney was highly respected by his many colleagues and patients. The citizens of Albany suffered a distinct loss by the death of Dr. Rooney and his passing away caused deep sorrow to his many friends and patients. He is survived by his wife, Mrs. Meredith H. Rooney and one son, Dr. John J. Rooney, F.A.C.P., of Boston, Mass.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,
Governor for Western New York

DR. ELLIOTT PLUMMER SMART

Elliott Plummer Smart, M.D., F.A.C.P., of Murphys, Calif., was born in Blue Earth, Minn., September 9, 1885. He received his M.D. degree from the University of Southern California School of Medicine in 1912.

During World War I, Dr. Smart served overseas in the Medical Corps, U. S. Army, as a Captain in the 157th Field Hospital. Following the war, he served with the U. S. Public Health Service and later with the Veterans' Bureau. From 1922 to 1936 Dr. Smart was Chief Resident Physician at the Olive View Sanatorium, Olive View, Calif. In 1936 he became associated with the Bret Harte Sanatorium, Murphys, Calif., where he was Medical Director and Superintendent. He was also Chief of the Tuberculosis Service of the San Joaquin General Hospital, French Camp, Calif.

In 1939 he was elected a Fellow of the American College of Physicians and became a Life Member of the College in 1945. Dr. Smart was a Past-President of

the American Sanatorium Association of California and the Calaveras County Tuberculosis Association. He was a Fellow of the American College of Chest Physicians and the American Trudeau Society.

Dr. Smart died in the San Joaquin General Hospital, October 13, 1950, of cerebral hemorrhage.

A quiet, unassuming physician, Dr. Smart was very well liked by his colleagues. He was devoted to his patients, devoted long hours to his work and in every respect was a true physician.

DWIGHT L. WILBUR, M.D., F.A.C.P.,
Governor for Northern California

DR. LEON STANLEY LIPPINCOTT

Leon Stanley Lippincott, M.D., F.A.C.P., of Daytona Beach, Fla., died unexpectedly of a pulmonary embolus on November 25, 1950. He was 62 years of age.

Born in Augusta, Maine, in 1888, Dr. Lippincott received an A.B. degree from Bowdoin College in 1910 and his M.D. from Bowdoin Medical School in 1913. He served as Instructor and Assistant Professor of Pathology and Bacteriology, Bowdoin Medical School from 1913 to 1917. During World War I he served with the Medical Corps, U. S. Army, and ended his military career as a Major and Chief of Laboratory Service, Base Hospital No. 72, overseas. After the war he went to Vicksburg, Miss., as Pathologist for the Vicksburg Sanitarium, 1919 to 1942. During World War II he returned to his native state and served as Pathologist for the Eastern Maine General Hospital, Bangor, Maine, until 1947. He then moved to Florida and became Pathologist and Director of the Clinical Laboratory for the Halifax District Hospital, Daytona Beach.

As a Masonic leader he was a Shriner and a member of the Scottish Rite and York Rite bodies. He served as Secretary-Treasurer, Vicksburg Masonic Temple, 1926–42, and one year as President and as Past Grand Master of the Grand Council of Mississippi. He was District Governor, 17th District, Rotary International, 1929–30, and was a member of the Elks Club and Past Exhalted Ruler in Vicksburg. He was active in the Daytona Beach Rotary Club and St. Mary's Episcopal Church.

Dr. Lippincott was elected a Fellow of the American College of Physicians in 1929 and became a Life Member in 1948. He was a Diplomate of the American Board of Pathology. He was also a Fellow of the American Society of Clinical Pathologists, the American Public Health Association and the American Medical Association. He was a member of the American Association of Pathologists and Bacteriologists, the American Association for the Advancement of Science, the American Association of Railway Surgeons, the Association of Military Surgeons of the United States, the Southern Medical Association, the New England Pathological Society, the Florida and Maine Medical Associations and the Volusia and Penobscot County Medical Associations.

NORMAN E. WILLIAMS, M.D.

DR. JOHN JOSEPH DUMPHY

John Joseph Dumphy, M.D., Sc.D. (Hon.), F.A.C.P., age 54, died suddenly December 19, 1950, in Worcester, Mass., of an acute myocardial infarction. He is survived by his widow, Irene Hennessy Dumphy.

A native of Springfield, Mass., he received an A.B. degree from Holy Cross College in 1917, and his M.D. degree from Harvard Medical School in 1921. His internships were spent at the St. Francis Hospital, Hartford, Conn., and at the Massachusetts General Hospital, Boston, Mass.

He practiced internal medicine in Worcester, Mass., from 1923 to the day of his death. In 1934 he was elected a Fellow of the American College of Physicians, and in 1938 was certified as a Diplomate of the American Board of Internal Medicine. In 1942 Holy Cross College conferred upon him the honorary degree of Doctor of Science. He was an active member of the Worcester District and Massachusetts State Medical Societies, having served as President of the District and Councillor of the State Society. He was a member of the Worcester City Advisory Health Board. For many years he was Physician, Chief of Medical Service, and Cardiologist at St. Vincent Hospital, Worcester, Mass. He was Consultant in Medicine at the Harrington Memorial Hospital, Southbridge, Mass.; the Webster District Hospital, Webster, Mass.; and the Milford Hospital, Milford, Mass.

Dr. Dumphy's modest, quiet, serious demeanor lightly covered an active, orderly mind and a sparkling wit. He was never assertive, pretentious or patronizing but had the happy faculty of having all of his young medical associates look upon him as their closest friend and advisor. He was a shining example of an ideal clinical internist who spent himself without reserve for his patients and his profession. His active life, dedicated to medicine and tragically terminated at the peak of his career, ennobled and enriched the profession. He will long be missed by his former patients, his fellow physicians and the community and county in general.

JAMES T. BROSNAN, M.D., F.A.C.P.

DR. HEINRICH ALBERT REYE

Heinrich Albert Reye, M.D., F.A.C.P., died on December 6, 1950, at the age of 64 of cerebral hemorrhage.

Dr. Reye was born in Germany on November 26, 1886, and came to the United States in early childhood. He graduated from the Riverside California High School and acquired his A.B. degree from the University of Michigan in 1910, and his M.D. from the University of Michigan Medical School in 1913. Following graduation and his resident training, he held several State and Municipal posts in psychiatric work. He was Clinical Director and Pathologist of the Pontiac State Hospital from 1914 to 1916; Neurologist to the Woman's Hospital and Infants Home in Detroit from 1916 to 1928; Neurologist at St. Mary's Hospital, 1919 to 1928. He was also Attending Neurologist for the City of Detroit Receiving Hospital and the United States Marine Hospital for many years; Professor and Director of the Neuropsychiatric Department, Wayne University College of Medicine from 1922 to 1946, then becoming Professor Emeritus.

Dr. Reye was a Diplomate of the American Board of Psychiatry and Neurology, a member of the American Psychoanalytical Society, the American Psychiatric Association, and was a Fellow of the American College of Physicians since 1928.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan